The present invention relates to fused bicyclic pyrimidine containing zinc-binding moiety based derivatives that have unique properties as protein tyrosine kinase (PTK) inhibitors and their use in the treatment of PTK related diseases and disorders such as cancer. The said derivatives may further act as HDAC inhibitors.
This application claims the benefit of U.S. Provisional Application No. 60/843,646, filed on Sep. 11, 2006 and U.S. Provisional Application No. 60/895,894, filed on Mar. 20, 2007. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life such as cell growth, differentiation, proliferation, cell cycle and survival, depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, there is a great deal of effort directed to identifying ways to modulate protein kinase activities.

Receptor tyrosine kinases ("RTKs") comprise a large family of transmembrane receptors with diverse biological activity. These receptors consist of a growth-factor-binding ectodomain, a single transmembrane segment, an intracellular protein-tyrosine kinase catalytic domain, and a tyrosine-containing cytoplasmic tail. At present, at least nineteen distinct subfamilies of RTKs have been identified. In the Split kinase family, an example of these is the subfamily platelet derived growth factor receptor ("PDGFR"), which includes PDGFRα, PDGFRβ, c-kit and c-fms. Another group which, because of its similarity to the PDGFR subfamily, is sometimes subsumed into the later group is the fett liver kinase (“fkt”) receptor subfamily. This group is believed to be made up of kinase insert domain-receptor fetal liver kinase-1 (KDR/Flk-1, VEGF-R2), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1). A further member of the tyrosine kinase receptor growth factor family is the vascular endothelial growth factor (VEGF) receptor subgroups. VEGF is presently thought to play an essential role is vasculogenesis and angiogenesis.

The ErbB/HER protein-tyrosine kinases family include ErbB1, ErbB2, ErbB3 and ErbB4. ErbB1, epidermal growth factor receptor (EGFR), and ErbB2 are overexpressed in a wide variety of tumors including breast, colorectal, ovarian, and non-small cell lung cancers. For example, overexpression of EGFR is present in at least 70% of human cancers (Seymour, L. K., "Carr Drug Targets" 2, 2001, 117-133) such as, non-small cell lung carcinomas (NSCLC), breast cancers, gliomas, squamous cell carcinoma of the head and neck, and prostate cancer (Raymond et al., "Drugs 60 Suppl 1, 2000, discussion 41-2; Salomon et al, "Critt Rev Oncol Hematol" 19, 1995, 183-232; Voldborg et al., "Ann Oncol" 8, 1997, 1197-1206). The EGFR-TK is therefore widely recognized as an attractive target for the design and development of compounds that can specifically bind and inhibit the tyrosine kinase activity and its signal transduction pathway in cancer cells, and thus can serve as either diagnostic or therapeutic agents. AEE-788, a member of the 7H-pyrollo[2,3] class of pyrimidines, is a novel orally available multi-tyrosine kinase receptor inhibitor that inhibits multiple targets including EGFR/ErbB2 and VEGF receptor tyrosine kinases. Its efficacy against a variety of tumors has been verified in preclinical animal models and human clinical trials. (Younes M., et al, "Clin Cancer Res.", 2006, 3425).

AEE-788 (NVP-AEE788)

Pyrimidine compounds, particularly fused pyrimidine compounds, make up one class of compounds known to inhibit certain tyrosine kinases. For example, U.S. Pat. No. 6,635,762 describes pyrrol[2,3-d]pyrimidine compounds. The compounds can be used to inhibit protein tyrosine kinases, especially Janus Kinase 3 (JAK3). U.S. Pat. No. 6,627,754 describes 4-aminopyrrol[2,3-d]pyrimidine compounds, where the amine is at least a secondary amine, that can be used to inhibit protein tyrosine kinases, especially Janus Kinase 3 (JAK3). The patent also discloses use of the compounds for treating diseases such as diabetes, cancer, autoimmune diseases, and the like.

Various pyrimidine compounds have also been identified as inhibitors of EGFR. U.S. Pat. No. 6,395,733 describes 4-aminopyrrol[2,3-d]pyrimidine compounds. U.S. Pat. No. 6,251,911 describes 4-amino-1H-pyrazolo[3,4-d]pyrimidine compounds having EGFR and c-erbB2 activity. U.S. Pat. Nos. 6,140,317, 6,140,332, 6,096,749, and 5,686,457 describe 4-aminopyrrol[2,3-d]pyrimidine compounds, 4-anilino pyrrolo[2,3-d]pyrimidine compounds, 4-anilino pyrrolo[2,3-d]pyrimidine compounds and 4-anilino pyrrolo[2,3-d]pyrimidine compounds respectively.

Furthermore, elucidation of the complex and multi-factorial nature of various diseases that involve multiple pathogenic pathways and numerous molecular components suggests that multi-targeted therapies may be advantageous over mono-therapies. Recent combination therapies with two or more agents for many such diseases in the areas of oncology, infectious disease, cardiovascular disease and other complex pathologies demonstrate that this combinatorial approach may provide advantages with respect to overcoming drug resistance, reduced toxicity and, in some circumstances, a synergistic therapeutic effect compared to the individual components.

Certain cancers have been effectively treated with such a combinatorial approach; however, treatment regimes using a cocktail of cytotoxic drugs often are limited by dose limiting toxicities and drug-drug interactions. More recent advances with molecularly targeted drugs have provided new approaches to combination treatment for cancer, allowing multiple targeted agents to be used simultaneously, or combining these new therapies with standard chemotherapeutics or radiation to improve outcome without reaching dose limiting toxicities. However, the ability to use such combinations currently is limited to drugs that show compatible pharmacologic and pharmacodynamic properties. In addition, the regulatory requirements to demonstrate safety and efficacy of combination therapies can be more costly and lengthy than corresponding single agent trials. Once approved, combination strategies may also be associated with increased costs to
patients, as well as decreased patient compliance owing to the more intricate dosing paradigms required. [0010] In the field of protein and polypeptide-based therapeutics it has become commonplace to prepare conjugates or fusion proteins that contain most or all of the amino acid sequences of two different proteins/polypeptides and that retain the individual binding activities of the separate proteins/polypeptides. This approach is made possible by independent folding of the component protein domains and the large size of the conjugates that permits the components to bind their cellular targets in an essentially independent manner. Such an approach is not, however, generally feasible in the case of small molecule therapeutics, where even minor structural modifications can lead to major changes in target binding and/or the pharmacokinetic/pharmacodynamic properties of the resulting molecule.

[0011] The use of EGFR inhibitors in combination with histone deacetylases (HDAC) has been shown to produce synergistic effects. Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed HDAC’s. HDAC’s are represented by X genes in humans and are divided into four distinct classes (J Mol Biol, 2004; 338:1, 17-31). In mammalian class I HDAC’s (HDAC1-3, and HDAC8) are related to yeast RPD3 HDAC, class II (HDAC4-7, HDAC9 and HDAC10) related to yeast HDA1, class 4 (HDAC11), and class 3 (a distinct class encompassing the sirtuins which are related to yeast Sir2).

[0012] Csordas, Biochem. J., 1990; 266: 23-38 teaches that histones are subject to post-translational acetylation of the ε-amino groups of N-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, access of transcription factors to chromatin templates is enhanced by histone hyperacetylation, and enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome (Taunton et al., Science, 1996; 272:408-411). In the case of tumor suppressor genes, transcriptional silencing due to histone modification can lead to oncogenic transformation and cancer.

[0013] Several classes of HDAC inhibitors currently are being evaluated by clinical investigators. The first FDA approved HDAC inhibitor is Suberoylanilide hydroxamic acid (SAHA, Zolinza®) for the treatment of cutaneous T-cell lymphoma (CTCL). Other HDAC inhibitors include hydroxamic acid derivatives, PXD101 and LAQ824, are currently in the clinical development. In the benzamide class of HDAC inhibitors, MS-275, MGCD0103 and CI-994 have reached clinical trials. Mourne et al. (Abstract #4725, AACR 2005), demonstrate that thiophenyl modification of benzamides significantly enhance HDAC inhibitory activity against HDAC1.

[0014] Recent advances suggest that PTK inhibitors in combination with HDAC inhibitors may provide advantageous results in the treatment of cancer. For example, co-treatment with SAHA significantly increased EGFR2 antibody trastuzumab-induced apoptosis of BT-474 and SKBR-3 cells and induced synergistic cytotoxic effects against the breast cancer cells (Bali, Clin. Cancer Res., 2005, 11, 3392). HDAC inhibitors, such as SAHA, have demonstrated synergistic antiproliferative and apoptotic effects when used in combination with gefitinib in head and neck cancer cell lines, including lines that are resistant to gefitinib monotherapy (Brizzese et al., Proc. AACR, 2004). Pretreating gefitinib resistant cell lines with the HDAC inhibitor, MS-275, led to a growth-inhibitory and apoptotic effect of gefitinib similar to that seen in gefitinib-sensitive NSCLC cell lines including those harboring EGFR mutations (Witta S. E., et al., Cancer Res, 2006, 66:2, 944-50). The HDAC inhibitor PXD101 has been shown to act synergistically to inhibit proliferation with the EGFR1 inhibitor Tarceva® (erlotinib) (WO2006082428A2).

[0015] The effects of combining AEI-788 and LBH589, a HDAC inhibitor, were evaluated in a number of cancer cell lines. Synergistic induction of apoptosis was observed after exposure of A549 (lung), MCF-7 (breast), Hela (cervical), OV202 (ovarian), Jurkat (acute T-cell leukemia), and K562 (chronic myelogenous leukemia) cells to a combination of AEI-788 and LBH589 (Yu C et al., 97th AACR, 2006).

[0016] Current therapeutic regimens of the types described above attempt to address the problem of drug resistance by the administration of multiple agents. However, the combined toxicity of multiple agents and/or drug-drug interaction often limits the effectiveness of this approach. Moreover, it often is difficult to combine compounds having differing pharmacokinetics into a single dosage form, and the consequent requirement of taking multiple medications at different time intervals leads to problems with patient compliance that can undermine the efficacy of the drug combinations. The development of novel agents that target multiple therapeutic targets selected not by virtue of cross reactivity, but through rational design will help improve patient outcome while avoiding these limitations. Enormous efforts are still directed to the development of selective anti-cancer drugs as well as to new and more efficacious compounds resulting from the modification of known anti-cancer drugs.

SUMMARY OF THE INVENTION

[0017] The present invention relates to fused bicyclic pyrimidine containing zinc-binding moiety based derivatives that have unique properties as protein tyrosine kinase (PTK) inhibitors and their use in the treatment of PTK related diseases and disorders such as cancer.

[0018] The compounds of the present invention may further act as HDAC or matrix metalloproteinase (MMP) inhibitors by virtue of their ability to bind zinc ions. Surprisingly these compounds are active at multiple therapeutic targets and are effective for treating disease. Moreover, in some cases it has even more surprisingly been found that the compounds have enhanced activity when compared to the activities of combinations of separate molecules individually having the PTK (EGFR, HER2/Erb2, VEGFR2) and HDAC activities. In other words, the combination of pharmacophores into a single molecule may provide a synergistic effect as compared to the individual pharmacophores. More specifically, it has been found that it is possible to prepare compounds that simultaneously contain a first portion of the molecule that binds zinc ions and thus permits inhibition of HDAC and/or matrix metalloproteinase (MMP) activity and at least a second portion of the molecule that permits binding to a separate and distinct target that inhibits multiple PTKs, particularly EGFR-TK, HER2/Erb2 and VEGFR2, and thus provides therapeutic benefit. Preferably, the compounds of the present invention inhibit PTK and HDAC activity.
Accordingly, the present invention provides a compound having the general formulae (I) and (II):

![Diagram](image)

where W is O or S; Y is absent, N or CH; Z is N or CH; R, and R₂ are independently hydrogen, OR, aliphatic or substituted aliphatic, wherein R is hydrogen, aliphatic, substituted aliphatic or acyl; provided that if R, and R₂ are both present, one of R, or R₂ must be OR and if Y is absent, R₂ must be OR; and R₈ is hydrogen, acyl, aliphatic or substituted aliphatic;
where Z, Y, and W are as previously defined; R₁₁ and R₁₂ are independently selected from hydrogen or aliphatic; R₁₁, R₁₂ and R₁₃ are independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkyaminio, substituted alkylaminio, dialkyaminio, substituted dialkyaminio, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonfyl, CF₃, CN, N₃, NO₂, sulfonyl, acyl, aliphatic, substituted aliphatic, aryl, substituted ary1, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

**DETAILED DESCRIPTION OF THE INVENTION**

[0027] In a first embodiment of the compounds of the present invention are compounds represented by formulae (I) and (II) as illustrated above, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof.

[0028] In a second embodiment of the compounds of the present invention are compounds represented by formula (III) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein n is 0-9; R′, Q, Ar and R₄ are as previously defined.

[0031] In a fourth embodiment of the compounds of the present invention are compounds represented by formula (V) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein n is 0-9; G is absent, O, S, SO₂, C(O)NH and N(Re); and R′, Q, Ar and R₄ are as previously defined.

[0032] In a fifth embodiment of the compounds of the present invention are compounds represented by formula (V) as illustrated below, or its geometric isomers, enantiomers,
diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein q is 0-6; m is 1-4; G is absent, O, S, SO, SO₂, and N(R₅); R', Q, Ar and R₅ are as previously defined.

[0033] In a sixth embodiment of the compounds of the present invention are compounds represented by formula (VII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein r is 1-10; U is N(R₅); Q, Ar and R₅ are as previously defined.

[0034] In a seventh embodiment of the compounds of the present invention are compounds represented by formula (VIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

[0036] Ar is aryl, substituted aryl heteroaryl or substituted heteroaryl;
[0037] Q is absent or substituted or unsubstituted alkyl;
[0038] X is O, S, NH, or alkylamino;
[0039] Z₂ is O, S, or NH;
[0040] Y is N or CR₂₀, where R₂₀ is selected from hydrogen, halogen, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

[0041] X₂ is either a direct bond or aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

[0042] B is a direct bond or straight- or branched-, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, aryalkyl, aryalkenyl, aryalkynyl, heteroaryloalkyl, heteroaryloalkenyl, heteroaryloalkynyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, alkylaryloalkyl, alkylaryloalkenyl, alkylaryloalkynyl, alkenylaryloalkenyl, alkenylaryloalkynyl, alkynylaryloalkenyl, alkynylaryloalkynyl, alkylheterearyloalkenyl, alkylheteroaryloalkynyl, alkenylheterearyloalkenyl, alkenylheterearyloalkynyl, alkynylheterearyloalkenyl, alkynylheterearyloalkynyl, alkylhetereocyclylalkenyl, alkylhetereocyclylalkynyl, alkylhetereocyclylalkenyl, alkylhetereocyclylalkynyl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R₄), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R₈ is hydrogen or aliphatic group;

[0043] C is selected from:

(a) [Image]

where W is O or S; Y is absent, N, or CH; Z is N or CH; R₁ and R₈ are independently hydrogen, hydroxy, aliphatic group, provided that if R₁ and R₈ are both present, one of R₁ or R₈ must be hydroxy and if Y is absent, R₈ must be hydroxy; and R₈ is hydrogen or aliphatic group;

(b) [Image]

where W is O or S; J is O, NH or NCH₃; and R₁₀ is hydrogen or lower alkyl;

[0045] wherein n is 0-9; and Q and Ar are as previously defined.

[0046] In a tenth embodiment of the compounds of the present invention are compounds represented by formula (XI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:
wherein $t$ is 1-9; $G$ is absent, O, S, SO₂, or N(R₆); Q, Ar and R₈ are as previously defined.

[0047] In an eleventh embodiment of the compounds of the present invention are compounds represented by formula (XII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein $n$ is 0-9; $G$ is absent, O, S, SO₂, and N(R₆); and Q, Ar and R₈ are as previously defined.

[0048] In a twelfth embodiment of the compounds of the present invention are compounds represented by formula (XIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein $q$ is 0-6; $m$ is 1-4; $G$ is absent, O, S, SO₂, and N(R₆); Q, Ar and R₈ are as previously defined.

[0049] In a thirteenth embodiment of the compounds of the present invention are compounds represented by formula (XIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

wherein $r$ is 1-10; $U$ is N(R₆); Q, Ar and R₈ are as previously defined.

[0050] Representative compounds according to the invention are those selected from the Table A below or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:
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The invention further provides methods for the prevention or treatment of diseases or conditions involving aberrant proliferation, differentiation, or survival of cells. In one embodiment, the invention further provides for the use of one or more compounds of the invention in the manufacture of a medicament for halting or decreasing diseases involving aberrant proliferation, differentiation, or survival of cells. In preferred embodiments, the disease is cancer. In one embodiment, the invention relates to a method of treating cancer in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), Hodgkin’s lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma. Further examples include myelodysplastic syndrome, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms’ tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal, nasopharyngeal and esophageal), gastrointestinal cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (e.g., small-cell and non small cell), breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, tumors related to Gorlin’s syndrome (e.g., medulloblastoma, meningioma, etc.), and liver cancer. Additional exemplary forms of cancer which may be treated by the subject compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer, anal cancer, rectal cancer, parathyroid cancer, and pituitary cancer.

Additional cancers that the compounds described herein may be useful in preventing, treating and studying are, for example, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharyngeal carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney (parenchyma carcinoma), cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroid melanoma, seminoma, rhabdomyosarcoma, craniofaryngioma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma. In one aspect of the invention, the present invention provides for the use of one or more compounds of the invention in the manufacture of a medicament for the treatment of cancer.

In one embodiment, the present invention includes the use of one or more compounds of the invention in the manufacture of a medicament that prevents further aberrant proliferation, differentiation, or survival of cells. For example, compounds of the invention may be useful in preventing tumors from increasing in size or from reaching a metastatic state. The subject compounds may be administered to halt the progression or advancement of cancer or to induce tumor apoptosis or to inhibit tumor angiogenesis. In addition, the instant invention includes use of the subject compounds to prevent a recurrence of cancer.

This invention further embraces the treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions. Dysplasia is the earliest form of pre-cancerous lesion recognizable in a biopsy by a pathologist. The subject compounds may be administered for the purpose of preventing said hyperplasias, dysplasias or pre-cancerous lesions from continuing to expand or
from becoming cancerous. Examples of pre-cancerous lesions may occur in skin, esophageal tissue, breast and cervical intra-epithelial tissue. [0056] “Combination therapy” includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the invention can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the invention. The compounds of the invention can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy. In general, a combination therapy envisioned administration of two or more drugs during a single cycle or course of therapy.

[0057] “Combination therapy” includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the invention can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the invention. The compounds of the invention can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy. In general, a combination therapy envisioned administration of two or more drugs during a single cycle or course of therapy.

[0058] In one aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate protein kinases involved in various disease states. Examples of such kinases may include, but are not limited to: serine/threonine specific kinases, receptor tyrosine specific kinases and non-receptor tyrosine specific kinases. Serine/threonine kinases include mitogen activated protein kinases (MAPK), meiosis specific kinase (MEK), RAF and auron kinase. Examples of receptor kinase families include epithelial growth factor receptor (EGFR) (e.g., HER2/neu, HER3, HER4, ErbB2, ErbB1, ErbB3, ErbB4), Erk1, Erk2), fibroblast growth factor (FGF) receptor (e.g., FGF-R1, FGF-R2, HER2/EGFR), erbB/HER, c-erbB2), KIT receptor, EGF-R, HER2, HER, Axl, c-Met, NTRK, RET). Tyrosine kinase family include include, but are not limited to, BCR-ABL (e.g., p3D1), ARG; BTK (e.g., ITK/EMT, Tec); CSK, FAK, FRS, JAK, SRC, BMX, FEGER, CDK and SYK.

[0059] In another aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate non-kinase biological targets or processes. Such targets include histone deacetylases (HDAC), DNA methyltransferase (DNMT), heat shock proteins (e.g., HSP90), and proteosomes.

[0060] In a preferred embodiment, subject compounds may be combined with antineoplastic agents (e.g. small molecules, monoclonal antibodies, antisense RNA, and fusion proteins) that inhibit one or more biological targets such as Zolinza, Tarceva, Iressa, Tykerb, Gleevec, Sutent, Sprycel, Nexavar, Sorafinib, CNF2024, RG108, BMS387052, Affinitak, Avastin, Herceptin, Erbitux, AG24322, PD325901, ZD6474, PD184322, Obatodax, ABL737 and AEF788. Such combinations may enhance therapeutic efficacy over efficacy achieved by any of the agents alone and may prevent or delay the appearance of resistant mutational variants.

[0061] In certain preferred embodiments, the compounds of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents encompass a wide range of therapeutic treatments in the field of oncology. These agents are administered at various stages of the disease for the purposes of shrinking tumors, destroying remaining cancer cells left over after surgery, inducing remission, maintaining remission and/or alleviating symptoms relating to the cancer or its treatment. Examples of such agents include, but are not limited to, alkylating agents such as mustard gas derivatives (Mechlorethamine, cyclophosphamide, chlorambucil, melphalan, ifosfamide), ethylenimines (thiotepa, hexamethylmelamine), Alkylsulfonates (Busulfan), Hydrazines and Triazines (Altretamine, Procabazine, Dacarbazine and Temozolomide), Nitrosoureas (Carmustine, Lomustine and Streptozocin), Ifosfamide and metal salts (Carboplatin, Cisplatin, and Oxaliplatin); plant alkaloids such as Podophyllotoxins (Etoposide and Teniposide), Taxanes (Paclitaxel and Docetaxel), Vinca alkaloids (Vincristine, Vinblastine, Vin- desine and Vindesin), and Campothecin analogs (Irinotecan and Topotecan); anti-tumor antibodies such as Chromomycins (Daunomycin and Placinycin), Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Valubicin and Iodarubicin), and miscellaneous antibodies such as Mitomycin, Actinomycin and Bleomycin; anti-metabolites such as folic acid antagonists (Metotrexate, Pemetrexed, Raltitrexed, Aminopterin), pyrimidine antagonists (5-Flouracil, Flouxuridine, Cytarabine, Capecitabine, and Gemcitabine), purine antagonists (6-Mercaptopurine and 6-Thioguanine) and adenosine deaminase inhibitors (Cladrabrine, Fludarabine, Mercaptopurine, Clorabine, Thioguanae, Nelarabine and Pentostatin); topoisomerase inhibitors such as topoisomerase I inhibitors (Ironotecan, topotecan) and topoisomerase II inhibitors (Amscarine, etopo- side, etoposide phosphate, teniposide); monoclonal antibod- ies (Alemtuzumab, Gentuzumab ozogamicin, Ritux- imab, Trastuzumab, Ibritumomab Tositomab, Cetuximab, Panitumumab, Tositumomab, Bevacizumab); and miscellaneous anti-neoplastic drugs such as ribonucleotide reductase inhibitors (Hydroxyurea); adrenocortical steroid inhibitors (Mitotane); enzymes (Asparaginase and Pegaspargase); anti-microtubule agents (Estramustine); and retinoids (Bexaro- tene, Isoretinoin, Tretinoin (ATRA)).

[0062] In certain preferred embodiments, the compounds of the invention are administered in combination with a chemoprotective agent. Chemoprotective agents act to protect the body or minimize the side effects of chemotherapy. Examples of such agents include, but are not limited to, antimetase, mesna, and dexrazoxane.

[0063] In one aspect of the invention, the subject compounds are administered in combination with radiation therapy. Radiation is commonly delivered internally (implanta- tion of radioactive material near cancer site) or externally from a machine that employs photon (x-ray or gamma-ray) or particle radiation. Where the combination therapy further comprises radiation treatment, the radiation treatment may be
conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0064] It will be appreciated that compounds of the invention can be used in combination with an immunotherapeutic agents. One form of immunotherapy is the generation of an active systemic tumor-specific immune response of host origin by administering a vaccine composition at a site distant from the tumor. Various types of vaccines have been proposed, including isolated tumor-antigen vaccines and anti-idiotypic vaccines. Another approach is to use tumor cells from the subject to be treated, or a derivative of such cells (reviewed by Schirmacher et al. (1995) J Cancer Res Clin Oncol. 121:487). In U.S. Pat. No. 5,484,596, Hanna Jr. et al. claim a method for treating a resectable carcinoma to prevent recurrence or metastases, comprising surgically removing the tumor, dispersing the cells with collagenase, irradiating the cells, and vaccinating the patient with at least three consecutive doses of about 10^7 cells.

[0065] It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more adjunctive therapeutic agents. Examples of suitable agents for adjunctive therapy include a 5HT1 agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an NK, antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; and DAMARD (e.g. meothetrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitriptyline); a neuron stabilizing anti-epileptic drug; a mono-amhogenic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumor necrosis factor alpha; an antibody therapy, such as a monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon); an opioid analgesics; a local anesthetic; a stimulant, including caffeine; an H3-antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide); an anti-emetic (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an antitussive (e.g. codeine, hydrocodone, dicyclomine, carbamazepine, or dextromethorphan); a diuretic, or a sedating or non-sedating antihistamine.

[0066] Matrix metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases collectively capable of degrading essentially all matrix components. Over 20 MMP modulating agents are in pharmaceutical develop, almost half of which are indicated for cancer. The University of Toronto researchers have reported that HDACs regulate MMP expression and activity in 3T3 cells. In particular, inhibition of HDAC by trichostatin A (TSA), which has been shown to prevent tumorigenesis and metastasis, decreases mRNA as well as zymographic activity of gelatinase A (MMP2; Type IV collagenase), a matrix metalloproteinase, which itself, implicated in tumorigenesis and metastasis (Ailenberg M., Silverman M., Biochem Biophys Res Commun. 2002, 298:110-115). Another recent article that discusses the relationship of HDAC and MMPs can be found in Young D. A., et al., Arthritis Research & Therapy. 2005, 7: 503. Furthermore, the commonality between HDAC and MMPs inhibitors is their zinc-binding functionality. Therefore, in one aspect of the invention, compounds of the invention can be used as MMP inhibitors and may be of use in the treatment of disorders relating to or associated with dysregulation of MMP. The overexpression and activation of MMPs are known to induce tissue destruction and are also associated with a number of specific diseases including rheumatoid arthritis, periodontal disease, cancer and atheriosclerosis.

[0067] The compounds may also be used in the treatment of a disorder involving, relating to or, associated with dysregulation of histone deacetylase (HDAC). There are a number of disorders that have been implicated by or known to be mediated at least in part by HDAC activity, where HDAC activity is known to play a role in triggering disease onset, or whose symptoms are known or have been shown to be alleviated by HDAC inhibitors. Disorders of this type that would be expected to be amenable to treatment with the compounds of the invention include the following but not limited to: Anti-proliferative disorders (e.g. cancers); Neurodegenerative diseases including Huntington’s Disease, Polyglutamine disease, Parkinson’s Disease, Alzheimer’s Disease, Seizures, Striatal neuronal degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesias, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Progressive supranuclear palsy, Pick’s disease, intracerebral hemorrhage. Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative Diseases of the Eye including Glaucoma, Age-related macular degeneration, Rubecotic glaucoma; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthritis, Crohn’s Disease, inflammatory bowel disease Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegren’s syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, mania, depression and dementia; Cardiovascular Diseases including heart failure, restenosis and arteriosclerosis; Fibrotic diseases including liver fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as Candida Albicans, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmaniasis infection, Trypanosoma brucei infection, Toxoplasmosis and coccidiosis and Haematopoeitic disorders including thalassemia, anemia and sickle cell anemia.

[0068] In one embodiment, compounds of the invention can be used to induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of the invention, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in
This document discusses various diseases and conditions, including:

- Disorders associated with apoptosis including cancer (particularly, but not limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including, but not limited to, herpes virus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including, but not limited to, systemic lupus, erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer’s disease, AIDS-related dementia, Parkinson’s disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDs, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including, but not limited to, chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

In one aspect, the invention provides the use of compounds of the invention for the treatment and/or prevention of immune response or immune-mediated responses and diseases, such as the prevention or treatment of rejection following transplantation of synthetic or organic grafting materials, cells, organs or tissue to replace all or part of the function of tissues, such as heart, kidney, liver, bone marrow, skin, cornea, vessels, lung, pancreas, intestine, limb, muscle, nerve tissue, duodenum, small-bowel, pancreatic-islet-cell, including xenotransplants, etc.; to treat or prevent graft-versus-host disease, autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, Hashimoto’s thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, juvenile-onset or recent-onset diabetes mellitus, uveitis, Graves disease, psoriasis, atopic dermatitis, Crohn’s disease, ulcerative colitis, vasculitis, auto-antibody mediated diseases, aplastic anemia, Evan’s syndrome, autoimmune hemolytic anemia, and the like; and further to treat infectious diseases causing aberrant immune response and/or activation, such as traumatic or pathogen induced immune disregulation, including for example, that which are caused by hepatitis B and C infections, HIV, staphylococcus aureus infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by an inflammatory response (e.g., leprosy); and to prevent or treat circulatory diseases, such as arteriosclerosis, atherosclerosis, vasculitis, polyarteritis nodosa and myocarditis. In addition, the present invention may be used to prevent/suppress an immune response associated with a gene therapy treatment, such as the introduction of foreign genes into autologous cells and expression of the encoded product. Thus in one embodiment, the invention relates to a method of treating an immune response disease or disorder or an immune-mediated response or disorder in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

In one aspect, the invention provides the use of compounds of the invention in the treatment of a variety of neurodegenerative diseases, a non-exhaustive list of which includes: I. Disorders characterized by progressive dementia in the absence of other prominent neurologic signs, such as Alzheimer’s disease; Senile dementia of the Alzheimer type; and Pick’s disease (lobar atrophy); II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington’s disease, Multiple system atrophy combining dementia with ataxia and/or manifestations of Parkinson’s disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentanigratal degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy); III. Syndromes of gradually developing abnormalities of posture and movement such as paralysis agitans (Parkinson’s disease), striatonigral degeneration, progressive supranuclear palsy, torsion dystonia (torsion spasm, dystonia muscularum deformans), spasmodic torticollis and other dyskinesias, familial tremor, and Gilles de la Tourette syndrome; IV. Syndromes of progressive ataxia such as cerebellar degenerations (e.g., cerebellar cortical degeneration and olivopontocerebellar atrophy (OPCA)); and spino-cerebellar degeneration (Friedreich’s ataxia and related disorders); V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome); VI. Syndromes of muscular weakness and wasting without sensory changes (motor neuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g., infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wolff-Jiurgelberg-Weislander) and other forms of familial spinal muscular atrophy), primary lateral sclerosis, and hereditary spastic paraplegia; VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies such as peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejereine-Sottas), and miscellaneous forms of chronic progressive neuropathy; VIII Syndromes of progressive visual loss such as pigmentary degeneration of the retina (retinitis pigmentosa), and hereditary optic atrophy (Leber’s disease). Furthermore, compounds of the invention can be implicated in chromat remodeling.

The invention encompasses pharmaceutical compositions comprising pharmaceutically acceptable salts of the compounds of the invention as described above. The invention also encompasses pharmaceutical compositions comprising hydrates of the compounds of the invention. The term “hydrate” includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate, and the like. The invention further encompasses pharmaceutical compositions comprising any solid or liquid physical form of the compound of the invention. For example, the compounds can be in a crystalline form, in an amorphous form, and have any particle size. The particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form.

The compounds of the invention, and derivatives, fragments, analogs, homologs, pharmaceutically acceptable salts or hydrate thereof can be incorporated into pharmaceutical compositions suitable for administration, together with a pharmaceutically acceptable carrier or excipient. Such compositions typically comprise a therapeutically effective amount of any of the compounds above, and a pharmaceutically acceptable carrier. Preferably, the effective amount when treating cancer is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.
Compounds of the invention may be administered by any suitable means, including, without limitation, parenteral, intravenous, intramuscular, subcutaneous, implantation, oral, sublingual, buccal, nasal, pulmonary, transdermal, topical, vaginal, rectal, and transmucosal administrations or the like. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Pharmaceutical preparations include a solid, semisolid or liquid preparation (tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, liquid, emulsion, suspension, syrup, injection etc.) containing a compound of the invention as an active ingredient, which is suitable for selected mode of administration. In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e., as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets, sachets and effervescent powders, and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the composition is formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the active compound and the inert carrier or diluent, a hard gelatin capsule.

Any inert excipient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulose material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium) and a lubricant (e.g., magnesium stearate), and may additionally comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof. Furthermore, the compositions of the present invention may be in the form of controlled release or immediate release formulations.

For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil. Solutions or suspensions can also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycercine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

In addition, the compositions may further comprise binders (e.g., acacia, corn starch, gelatin, caromer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., corn starch, potato starch, alginic acid, silicone dioxide, crosscarmellose sodium, crospovidone, guar gum, sodium starch glycolate, Primogel), buffers (e.g., tris-HCl, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g., sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycol, cyclodextrins), a glidant (e.g., colloidal silicon dioxide), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g., carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g., sucrose, aspartame, citric acid), flavoring agents (e.g., peppermint, methyl salicylate, or orange flavoring), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polychloroethers, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

It is especially advantageous to formulate oral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Daily administration may be repeated continuously for a period of several days to several years. Oral treatment may continue for between one week and the life of the patient. Preferably the administration may take place for five consecutive days after which time the patient can be evaluated to determine if further administration is required. The administration can be continuous or intermittent, i.e., treatment for a number of consecutive days followed by a rest period. The
compounds of the present invention may be administered intravenously on the first day of treatment, with oral administra-
tion on the second day and all consecutive days thereaf-
ter.

[0081] The preparation of pharmaceutical compositions
that contain an active component is well understood in the art,
for example, by mixing, granulating, or tablet-forming pro-
cesses. The active therapeutic ingredient is often mixed with
excipients that are pharmaceutically acceptable and compat-
ible with the active ingredient. For oral administration, the
active agents are mixed with additives customary for this
purpose, such as vehicles, stabilizers, or inert diluents, and
converted by customary methods into suitable forms for
administration, such as tablets, coated tablets, hard or soft
gelatin capsules, aqueous, alcoholic or oily solutions and the
like as detailed above.

[0082] The amount of the compound administered to the
patient is less than an amount that would cause toxicity in the
patient. In certain embodiments, the amount of the compound
that is administered to the patient is less than the amount
that causes a concentration of the compound in the patient’s
plasma to equal or exceed the toxic level of the compound.
Preferably, the concentration of the compound in the patient’s
plasma is maintained at about 10 nM. In one embodiment, the
concentration of the compound in the patient’s plasma is
maintained at about 25 nM. In one embodiment, the concen-
tration of the compound in the patient’s plasma is maintained
at about 50 nM. In one embodiment, the concentration of the
compound in the patient’s plasma is maintained at about
100 nM. In one embodiment, the concentration of the compound
in the patient’s plasma is maintained at about 500 nM. In one
embodiment, the concentration of the compound in the patient’s
plasma is maintained at about 1000 nM. In one embodiment, the
concentration of the compound in the patient’s plasma is
maintained at about 2500 nM. In one embodiment, the concen-
tration of the compound in the patient’s plasma is maintained at
about 5000 nM. The optimal amount of the compound that should be administered to the
patient in the practice of the present invention will depend on
the particular compound used and the type of cancer being
treated.

DEFINITIONS

[0083] Listed below are definitions of various terms used
to describe this invention. These definitions apply to the terms
as they are used throughout this specification and claims, unless
otherwise limited in specific instances, either individually or
as part of a larger group.

[0084] An “aliphatic group” or “aliphatic” is non-aromatic
moiety that may be saturated (e.g. single bond) or contain one
or more units of unsaturation, e.g., double and/or triple bonds.
An aliphatic group may be straight chained, branched or
cyclic, contain carbon, hydrogen or, optionally, one or more
heteroatoms and may be substituted or unsubstituted. An
aliphatic group preferably contains between about 1 and
about 24 atoms, more preferably between about 4 to about 24
atoms, more preferably between about 4 to 12 atoms, more
typically between about 4 and about 8 atoms.

[0085] The term “acyl” refers to hydrogen, alkyl, partially
saturated or fully saturated cycloalkyl, partially saturated or
fully saturated heterocycle, aryl, and heteroaroyl substituted
carbonyl groups. For example, acyl includes groups such as
(C1–C6)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl,
valeryl, caproyl, 1-butylyacetel, etc.), (C3–C6)cycloalkylcarbonyl
(e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclo-
pentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic car-

[0086] The term “alkyl” embraces linear or branched rad-
icals having one to about twenty carbon atoms or, preferably,
two to about twelve carbon atoms. More preferred alkyl radi-
cals are “lower alkyl” radicals having one to about ten carbon
atoms. Most preferred are lower alkyl radicals having one to
about eight carbon atoms. Examples of such radicals include
methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-bu-
tyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0087] The term “alkenyl” embraces linear or branched rad-
icals having at least one carbon-carbon double bond of two
to about twenty carbon atoms or, preferably, two to about
twelve carbon atoms. More preferred alkenyl radicals are
“lower alkenyl” radicals having two to about ten carbon
atoms and more preferably about two to about eight carbon
atoms. Examples of alkenyl radicals include ethenyl, allyl,
propenyl, butenyl and 4-methylbutenyl. The terms “alkenyl”,
and “lower alkenyl”, embrace radicals having “cis” and
“trans” orientations, or alternatively, “E” and “Z” orienta-
tions.

[0088] The term “alkynyl” embraces linear or branched rad-
icals having at least one carbon-carbon triple bond of two
to about twenty carbon atoms or, preferably, two to about
twelve carbon atoms. More preferred alkynyl radicals are
“lower alkynyl” radicals having two to about ten carbon
atoms and more preferably about two to about eight carbon
atoms. Examples of alkynyl radicals include propargyl,
1-propynyl, 2-propynyl, 1-butynyl and 1-pentynyl.

[0089] The term “cycloalkyl” embraces saturated carbocyclic
radicals having three to about twelve carbon atoms. The
term “cycloalkyl” embraces saturated carbocyclic radicals
having three to about twelve carbon atoms. More preferred
cycloalkyl radicals are “lower cycloalkyl” radicals having
to about eight carbon atoms. Examples of such radicals include
cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0090] The term “cycloalkenyl” embraces partially unsat-
urated carbocyclic radicals having three to twelve carbon
atoms. Cycloalkenyl radicals that are partially unsaturated
carbocyclic radicals that contain two double bonds (that may
or may not be conjugated) can be called “cycloalkenylidenyl”.
More preferred cycloalkenyl radicals are “lower cyclo-
alkenyl” radicals having four to about eight carbon atoms.
Examples of such radicals include cyclobutenyl, cyclopenten-
yl and cyclohexenyl.

[0091] The terms “alkoxy” embrace linear or branched
oxy-containing radicals each having alkoxy portions of one to
about twenty carbon atoms or, preferably, one to about twenty carbon atoms. More preferred alkoxy radicals are “lower alkoxy” radicals having one to about ten carbon atoms and more preferably having one to about eight carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0092] The term “alkoxyalkyl” embraces alkylic radicals having one or more alkoxy radicals attached to the alkylic radical, that is, to form monoalkoxyalkyl and dialk oxylalkyl radicals.

[0093] The term “aryl”, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term “aryl” embraces aromatic radicals such as phenyl, naphtyl, tetralyndronaphthyl, indane and biphenyl.

[0094] The term “carbonyl”, whether used alone or with other terms, such as “alkoxy carbonyl”, denotes (C=O).

[0095] The term “carbanoyl”, whether used alone or with other terms, such as “arylcarbanoyl alkyl”, denotes C(O)NH.

[0096] The terms “heterocyclic”, “heterocyclic” or “heterocyclic” or “heteroaromatic” embrace saturated, partially unsaturated and unsaturated heteratom-containing ring-shaped radicals, which can also be called “heterocyclic”, “heterocyc loalkenyl” and “heteroaryl” correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heterocyclic monocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heterocyclic monocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, etc.); saturated 3 to 6-membered heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclic radicals include dihydrothiophene, dihydrofuran, dihydrofuran and dihydrothiazole. Heterocyclic radicals may include a pentavalent nitrogen, such as in tetrazolium and pyrimidin radicals. The term “heterocyclic” also embraces radicals where heterocyclic radicals are fused with aryl or cycloalkyl radicals. Examples of such fused bicyclic radicals include benzofuran, benzo thiophene, and the like.

[0097] The term “heteroaryl” embraces unsaturated heteroaryl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6-membered heterocyclic monocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrol, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, triazinyl, triazolyl (e.g., 1H-1,2,3-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g., 1H-tetrazolyl, 1H-tetrazolyl, etc., etc.); unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinylyl, benzimidazolyl, quinolino, isoquinolino, indazolyl, benzoindazolyl, tetrazolopyridazinyl (e.g., tetrazaolyl, 1-b-pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heterocyclic monocyclic group containing an oxygen atom, for example, pyranol, furan, etc.; unsaturated 3 to 6-membered heterocyclic monocyclic group containing a sulfur atom, for example, thiennyl, etc.; unsaturated 3 to 6-membered heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxa diazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoazolyl, benzoazazolyl, etc.); unsaturated 3 to 6-membered heterocyclic monocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like.

[0098] The term “heterocycloalkyl” embraces heterocycloalkyl substituted alkylic radicals. Most preferred heterocycloalkyl radicals are “lower heterocycloalkyl” radicals having one to six carbon atoms and a heterocycloalkyl radicals.

[0099] The term “alkylthio” embraces radicals containing a linear or branched alkyl radical attached to a divalent sulfur atom. Preferred alkylthio radicals have alkyl radicals of one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylthio radicals have alkyl radicals of one to about ten carbon atoms. Most preferred are alkylthio radicals having lower alkyl radicals of one to about eight carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0100] The terms “aryalkyl” or “arylalkyl” embrace aryl substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl.

[0101] The term “aryloxy” embraces aryl radicals attached through an oxygen atom to other radicals.

[0102] The terms “aryalkoxy” or “arylylalkoxy” embrace arylalkyl radicals attached through an oxygen atom to other radicals.

[0103] The term “amin alkyl” embraces alkyl radicals substituted with amino radicals. Preferred amin alkyl radicals have alkyl radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred amin alkyl radicals are “lower amin alkyl” that have alkyl radicals having one to about ten carbon atoms. Most preferred are amin alkyl radicals having lower alkyl radicals having one to eight carbon atoms. Suitable lower alkylamines may be monosubstituted N-alkylamin o or disubstituted N,N-alkylamine, such as N-methyl-N-ethylamine, N,N-dimethylamine, N,N-diethylamine or the like.

[0104] The term “alkylamino” denotes amino groups which are substituted with one or two alkyl radicals. Preferred alkylamin o radicals have alkyl radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylamin o radicals are “lower alkylamin o” that have alkyl radicals having one to about ten carbon atoms. Most preferred are alkylamin o radicals having lower alkyl radicals having one to about eight carbon atoms. Suitable lower alkylamines may be monosubstituted N-alkylamin o or disubstituted N,N-alkylamine, such as N-methyl-N-ethylamine, N,N-dimethylamine, N,N-diethylamine or the like.

[0105] The term “linker” means an organic moiety that connects two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR₂, C(O), C(O)NH, SO₂, SO₅, or a chain of atoms, such as substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, aryalkyl, arylalkenyl, arylalkynyl, heteroarylalkenyl, heteroarylalkynyl, heterocycloalkenyl, heterocycloalkynyl, aryl, heteroaryl, heterocycle, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylaryalkenyl, alkylaryalkynyl, alkylarylenyl, alkenylarylenyl, alkynylarylenyl.
The term “angiogenesis,” as used herein, refers to the formation of blood vessels. Specifically, angiogenesis is a multi-step process in which endothelial cells locally degrade and invade through their own basement membrane, migrate through interstitial stroma toward an angiogenic stimulus, proliferate proximal to the migrating tip, organize into blood vessels, and reattach to newly synthesized basement membrane (see Folkman et al., Adv. Cancer Res., Vol. 43, pp. 175-203 (1985)). Anti-angiogenic agents interfere with this process. Examples of agents that interfere with several of these steps include thrombospordin-1, angiostatin, endostatin, interferon alpha and compounds such as matrix metalloproteinase (MMP) inhibitors that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as alpha.v.beta.3 inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor; agents, such as specific COX-2 inhibitors, that prevent the growth of cells that form new blood vessels; and protein-based compounds that simultaneously interfere with several of these targets.

The term “apoptosis” as used herein refers to programmed cell death as signaled by the nuclei in normally functioning human and animal cells when age or state of cell health and condition dictates. An “apoptosis inducing agent” triggers the process of programmed cell death.

The term “cancer” as used herein denotes a class of diseases or disorders characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis.

The term “compound” is defined herein to include pharmaceutically acceptable salts, solvates, hydrates, polymorphs, enantiomers, diastereoisomers, racemates and the like of the compounds having a formula as set forth herein.

The term “devices” refers to any appliance, usually mechanical or electrical, designed to perform a particular function.

As used herein, the term “dysplasia” refers to abnormal cell growth.

The term “hyperplasia,” as used herein, refers to excessive cell division or growth.

The phrase an “immunotherapeutic agent” refers to agents used to transfer the immunity of an immune donor, e.g., another person or an animal, to a host by inoculation. The term embraces the use of serum or gamma globulin containing performed antibodies produced by another individual or an animal; nonspecific systemic stimulation; adjuvants; active specific immunotherapy; and adoptive immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by therapy or agents that include host inoculation of sensitized lymphocytes, transfer factor, immune RNA, or antibodies in serum or gamma globulin.

The term “inhibition,” in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

The term “metastasis,” as used herein, refers to the migration of cancer cells from the original tumor site through...
the blood and lymph vessels to produce cancers in other tissues. Metastasis also is the term used for a secondary cancer growing at a distant site.

[0121] The term “neoplasm,” as used herein, refers to an abnormal mass of tissue that results from excessive cell division. Neoplasms may be benign (not cancerous), or malignant (cancerous) and may also be called a tumor. The term “neoplasia” is the pathological process that results in tumor formation.

[0122] As used herein, the term “pre-cancerous” refers to a condition that is not malignant, but is likely to become malignant if left untreated.

[0123] The term “proliferation” refers to cells undergoing mitosis.

[0124] The phrase “PTK related disease or disorder” refers to a disease or disorder characterized by inappropriate PTK activity or over-activity of the PTK. Inappropriate activity refers to either, (i) PTK expression in cells which normally do not express PTKit; (ii) increased PTK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (iii) decreased PTK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of PTKs refers to either amplification of the gene encoding a particular PTK or production of a level of PTK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PTK increases, the severity of one or more of the symptoms of the cellular disorder increases). Over activity can also be the result of ligand independent or constitutive activation as a result of mutations such as deletions of a fragment of a PTK responsible for ligand binding.

[0125] The phrase a “radiotherapeutic agent” refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia.

[0126] The term “recurrence” as used herein refers to the return of cancer after a period of remission. This may be due to incomplete removal of cells from the initial cancer and may occur locally (the same site of initial cancer), regionally (in vicinity of initial cancer, possibly in the lymph nodes or tissue), and/or distally as a result of metastasis.

[0127] The term “treatment” refers to any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal’s condition, directly or indirectly.

[0128] The term “vaccine” includes agents that induce the patient’s immune system to mount an immune response against the tumor by attacking cells that express tumor associated antigens (TAs).

[0129] As used herein, the term “effective amount of the subject compounds,” with respect to the subject method of treatment, refers to an amount of the subject compound which, when delivered as part of desired dose regimen, brings about, e.g., a change in the rate of cell proliferation and/or state of differentiation and/or rate of survival of a cell to clinically acceptable standards. This amount may further relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

[0130] As used herein, the term “pharmacologically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmacologically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmacologically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid or inorganic acid. Examples of pharmacologically acceptable nontoxic acid addition salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid lactobioninic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmacologically acceptable salts include, but are not limited to, adipate, aspartate, asparagine, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclpentanepropionate, dglucuronate, dodecylsulfate, ethanesulfonate, formate, fumarate, gluconate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmiante, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and aminocations formed using counterions such as halide, hydroxide, carbonate, sulfate, phosphate, nitrate, and alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

[0131] As used herein, the term “pharmacologically acceptable ester” refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmacologically acceptable aliphatic carboxylic acids, particularly alkanioic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

[0132] The term “pharmacologically acceptable prodrugs” as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as thewitterionic forms, where possible, of the compounds of the present invention. “Prodrug”, as used herein means a compound which is convertible in vivo by metabolic

[0133] As used herein, “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonics and absorption delaying agents, and the like, compatible with pharmaceutical administration, such as sterile pyrogen-free water. Suitable carriers are described in the most recent edition of Remington’s Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, buffer solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically acceptable substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0134] As used herein, the term “pre-cancerous” refers to a condition that is not malignant, but is likely to become malignant if left untreated.

[0135] The term “subject” as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

[0136] The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, after metabolism and alter rate of excretion.

[0137] The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formula herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2d Ed.; John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser’s Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

[0138] The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, or other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers or cis- and trans-isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as trans may be cis, trans, or a mixture of the two in any proportion.

Pharmaceutical Compositions

[0139] The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

[0140] As used herein, the term “pharmaceutically acceptable carrier or excipient” means a non-toxic, inert solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; cyclodextrins such as alpha-(α), beta- (β) and gamma- (γ) cyclodextrins; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycerol such as propylene glycol; esters such as ethyl oleate and ethyl laureate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0141] The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an
implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional nontoxic pharmaceutically acceptable carriers, adjutants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intrarticular, intraarterial, intrasynovial, intradermal, intrathecal, intraesophageal and intracranial injection or infusion techniques.

[0142] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butanediol glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0143] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0144] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0145] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsulate matrices of the drug in biodegradable polymers such as poly(lactide-co-glycolide). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

[0146] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0147] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethyl cellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetostearyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0148] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0149] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0150] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

[0151] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins,
starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, t alc and zinc oxide, or
mixtures thereof.

[0152] Powders and sprays can contain, in addition to the
compounds of this invention, excipients such as lactose, talc,
silicic acid, aluminum hydroxide, calcium silicates and
polyamide powder, or mixtures of these substances. Sprays
can additionally contain customary propellants such as chlo-
rofluorohydrocarbons.

[0153] Transdermal patches have the added advantage of
providing controlled delivery of a compound to the body. Such
dosage forms can be made by dissolving or dispensing the
compound in the proper medium. Absorption enhancers
then be used to increase the flux of the compound across
the skin. The rate can be controlled by providing a rate
controlling membrane or by dispersing the compound in a
polymer matrix or gel.

[0154] For pulmonary delivery, a therapeutic composition of
the invention is formulated and administered to the patient
in solid or liquid particulate form by direct administration
e.g., inhalation into the respiratory system. Solid or liquid
particulate forms of the active compound prepared for prac-
ticing the present invention include particles of respirable
size: that is, particles of a size sufficiently small to pass
t through the mouth and larynx upon inhalation and into the
bronchi and alveoli of the lungs. Delivery of aerosolized
therapeutics, particularly aerosolized antibiotics, is known in
the art (see, for example U.S. Pat. No. 5,767,006 to VanDe-
vanter et al., U.S. Pat. No. 5,508,259 to Smith et al., and WO
98/43,650 by Montgomery, all of which are incorporated
herein by reference). A discussion of pulmonary delivery of
antibiotics is also found in U.S. Pat. No. 6,014,969, incorpo-
rated herein by reference.

[0155] By a “therapeutically effective amount” of a com-
 pound of the invention is meant an amount of the compound
which confers a therapeutic effect on the treated subject, at
a reasonable benefit/risk ratio applicable to any medical treat-
ment. The therapeutic effect may be objective (i.e., measur-
able by some test or marker) or subjective (i.e., subject gives
an indication of or feels an effect). An effective amount of the
compound described above may range from about 0.1 mg/Kg
to about 500 mg/Kg, preferably from about 1 to about 50
mg/Kg. Effective doses will also vary depending on route of
administration, as well as the possibility of co-usage with
other agents. It will be understood, however, that the total
daily dosage of the compounds and compositions of the
present invention will be decided by the attending physician
within the scope of sound medical judgment. The specific
therapeutically effective dose level for any particular patient
will depend upon a variety of factors including the disorder
being treated and the severity of the disorder; the activity of
the specific compound employed; the specific composition
employed; the age, body weight, general health, sex and diet
of the patient; the time of administration, route of adminis-
tration, and rate of excretion of the specific compound
employed; the duration of the treatment; drugs used in combi-
nation or contemporaneously with the specific compound
employed; and like factors well known in the medical arts.

[0156] The total daily dose of the compounds of this inven-
tion administered to a human or other animal in single or in
divided doses can be in amounts, for example, from 0.01 to 50
mg/kg body weight or more usually from 0.1 to 25 mg/kg
body weight. Single dose compositions may contain such
amounts or submultiples thereof to make up the daily dose. In
general, treatment regimens according to the present inven-
tion comprise administration to a patient in need of such
treatment from about 10 mg to about 1000 mg of the com-
 pound(s) of this invention per day in single or multiple doses.

[0157] The compounds of the formulas described herein
can, for example, be administered by injection, intravenously,
intraaurally, subcutaneously, intraperitoneally, intramuscu-
larly, or subcutaneously; or orally, buccally, nasally, transmu-
sosally, topically, in an ophthalmic preparation, or by inhala-
tion, with a dosage ranging from about 0.1 to about 500 mg/kg
of body weight, alternatively dosages between 1 mg and 1000
mg/dose, every 4 to 120 hours, or according to the require-
ments of the particular drug. The methods herein contemplate
administration of an effective amount of compound or com-
 pound composition to achieve the desired or stated effect.
Typically, the pharmaceutical compositions of this invention
will be administered from about 1 to about 6 times per day or
alternatively, as a continuous infusion. Such administration
can be used as a chronic or acute therapy. The amount of
active ingredient that may be combined with pharmaceuti-
cally excipients or carriers to produce a single dosage form
will vary depending upon the host treated and the particular
mode of administration. A typical preparation will contain
from about 5% to about 95% active compound (w/w). Alter-
natively, such preparations may contain from about 20% to
about 80% active compound.

[0158] Lower or higher doses than those recited above may
be required. Specific dosage and treatment regimens for any
particular patient will depend upon a variety of factors,
including the activity of the specific compound employed,
the age, body weight, general health status, sex, diet, time of
administration, rate of excretion, drug combination, the severity
and course of the disease, condition or symptoms, the
patient’s disposition to the disease, condition or symptoms,
and the judgment of the treating physician.

[0159] Upon improvement of a patient’s condition, a main-
tenance dose of a compound, composition or combination of
this invention may be administered, if necessary. Subse-
quently, the dosage or frequency of administration, or both,
may be reduced, as a function of the symptoms, to a level at
which the improved condition is retained when the symptoms
have been alleviated to the desired level. Patients may, how-
ever, require intermittent treatment on a long-term basis upon
any recurrence of disease symptoms.

Synthetic Methods

[0160] The compounds of the invention may be prepared by
any process known to be applicable to the preparation of
chemically-related compounds. Suitable processes for mak-
ing certain intermediates include, for example, those illus-
trated in patent publications WO97/02266, US2004/0248911
essary starting materials may be obtained by standard pro-
cedures of organic chemistry. The preparation of such starting
materials is described within the accompanying non-limiting
Examples. Alternatively necessary starting materials are
obtainable by analogous procedures to those illustrated which
are within the ordinary skill of a chemist.

[0161] The compounds and processes of the present inven-
tion will be better understood in connection with the follow-
ings representative synthetic scheme that illustrate the meth-
ods by which the compounds of the invention may be
prepared, which are intended as an illustration only and not
limiting of the scope of the invention.
[0162] The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or
methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1

Preparation of (R)—N-hydroxy-2-(4-(4-ethyl-phenyl)-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)acetic (Compound 17)

Step 1a. Ethyl 2-amino-5-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate (Compound 402)

[0163] To the solution of EtOAc (4.08 g, 60 mmol) in EtOH (60 mL) was added compound 104 (10.6 g, 60 mmol) at 0°C. Under nitrogen. The mixture was stirred for 20 minutes and 2-bromo-4'-methoxyacetophenone was added. After stirring at room temperature overnight, the mixture was concentrated and the residue was taken up in ethyl acetate, washed with water and brine, and concentrated to give a residue which was purified by column chromatography to afford the product 402 as a solid (5.2 g, 67% yield). H NMR (DMSO-d6) δ 10.62 (s, 1H), 7.41 (d, J=6.6 Hz, 2H), 6.88 (d, J=6.6 Hz, 2H), 6.50 (d, J=3.0 Hz, 1H), 5.59 (s, 2H), 4.13 (q, J=6.9 Hz, 2H), 3.74 (s, 3H), 1.24 (t, J=7.2 Hz, 3H). LC-MS: 260 (M+1).

Step 1b. 6-(4-Methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Compound 403)

[0164] A mixture of compound 402 (4.7 g, 18 mmol), formamide (30 mL), formic acid (7.0 mL) and N,N-dimethylformamide (15 mL) was heated to 150°C. Overnight. The mixture was cooled to room temperature and filtered, washed with i-PrOH, EtOAc successively to give the product 403 as a solid (3.7 g, 86% yield). H NMR (DMSO-d6) δ 12.22 (s, 1H), 11.81 (s, 1H), 7.84 (s, 1H), 7.76 (d, J=6.6 Hz, 2H), 6.98 (d, J=6.6 Hz, 2H), 6.29 (d, J=2.4 Hz, 1H), 3.78 (s, 3H). LC-MS: 241 (M+1).

Step 1c. 4-Chloro-6-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine (Compound 404)

[0165] To a flask containing compound 403 (4.0 g, 16.7 mmol) was added POCl3 (32 mL) and the mixture was heated to reflux for 2 h. The mixture was cooled and poured into ice-water. NaOH was added to pH 7. The aqueous layer was extracted with ethyl acetate (250 mL×4). The combined organic layer was washed with brine, dried and concentrated to afford the product 404 as a yellow solid (2.2 g, 50% yield). Combined organic layer was washed with water, brine, and concentrated to give a residue which was purified by column chromatography to afford the product 404 as a white solid (40 mg, 32% yield). H NMR (DMSO-d6) δ 12.95 (s, 1H), 8.55 (s, 1H), 7.98 (d, J=6.9 Hz, 2H), 7.07 (d, J=6.9 Hz, 2H), 6.98 (d, J=2.1 Hz, 1H), 3.82 (s, 3H). LC-MS: 260 (M+1).

Step 1d. (R)-6-(4-Methoxyphenyl)-N-(1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 405)

[0166] A mixture of compound 404 and (R)-(α)-alpha-methylbenzylamine (2.23 g, 2.5 equiv) was added to n-BuOH and the resulting mixture was heated to 145°C overnight. Then another portion of (R)-(α)-alpha-methylbenzylamine (440 mg, 0.5 equiv) was added to the reaction mixture. The mixture was cooled, filtered, washed with Et2O to afford the product 405 as a yellow solid (1.8 g, 70% yield). H NMR (DMSO-d6) δ 11.88 (s, 1H), 8.01 (s, 1H), 7.68-7.71 (m, 3H), 7.39-7.42 (m, 2H), 7.25-7.30 (m, 2H), 7.17-7.19 (m, 1H), 6.93-7.01 (m, 2H), 5.49-5.51 (m, 1H), 3.77 (s, 3H), 1.51 (d, J=6.9 Hz, 3H). LC-MS: 345 (M+1).

Step 1e. (R)-4-(4-(1-Phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (Compound 406)

[0167] To a solution of compound 405 (1.13 g, 3.0 mmol) in dichloromethane (80 mL) was added dropwise the solution of BBr3 (3.0 mL) in dichloromethane (100 mL) at 0°C under nitrogen over 1 h. After the addition was completed, the mixture was allowed to warm to room temperature and stirred for another 5 h. Then 20 mL of water was added. The aqueous layer was extracted with ethyl acetate (100 mL×3), washed with brine, concentrated to give the product 406 as a solid (500 mg, 51% yield). H NMR (DMSO-d6) δ 13.09 (s, 1H), 9.76 (br, 1H), 8.38 (d, J=3.6 Hz, 1H), 7.68-7.73 (m, 3H), 7.55-7.57 (m, 2H), 7.43-7.48 (m, 2H), 7.34-7.39 (m, 1H), 6.94-6.96 (m, 2H), 5.49-5.50 (m, 1H), 1.73 (d, J=6.9 Hz, 3H). LC-MS: 331 (M+1).

Step 1f. (R’)-Ethyl 2-(4-(1-Phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)acetate (Compound 407)

[0168] To a mixture of compound 406 (100 mg, 0.3 mmol) and K2CO3 (70 mg, 0.5 mmol) in dimethylformamide (1.0 mL) was added ethyl 2-bromoacetoate (50 mg, 0.3 mmol) and the mixture was stirred at room temperature for 20 h. 5 mL of water was added and the mixture was extracted with ethyl acetate (25 mL×4), dried and concentrated to give a residue which was purified by column chromatography to afford the product 407 as a white solid (40 mg, 32% yield). H NMR (DMSO-d6) δ 11.89 (s, 1H), 8.01 (s, 1H), 7.67-7.72 (m, 3H), 7.39-7.42 (d, J=8.1 Hz, 2H), 7.25-7.31 (m, 2H), 7.17-7.20 (m, 1H), 6.94-7.00 (m, 2H), 5.46-5.48 (m, 1H), 4.80 (s, 2H), 4.16 (q, J=6.9 Hz, 2H), 1.51 (d, J=6.9 Hz, 3H), 1.20 (t, J=7.2 Hz, 3H). LC-MS: 417 (M+1).

Step 1g. (R)—N-Hydroxy-2-(4-(1-Phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)acetamide (Compound 17)

[0169] Preparation of the solution of hydroxylamine in methanol: hydroxylamine hydrochloride (4.67 g, 67 mmol) was dissolved in methanol (24 mL) made to solution A. Potassium hydroxide (5.61 g, 100 mmol) was dissolved in methanol (14 mL) made to solution B. The solution A was cooled to 0°C, and solution B was added into solution A dropwise. The mixture was stirred for 30 minutes at 0°C, and was allowed to stand at low temperature for some time. The precipitate was isolated to afford the solution of hydroxylamine in methanol.

[0170] To a flask containing compound 407-17 (35 mg, 0.084 mmol) was added the above solution of hydroxylamine in methanol (2.0 mL). The mixture was stirred at room temperature for 30 min. Then it was adjusted to pH 7 using concentrated HCl. The mixture was concentrated to give a residue which was purified by column chromatography to afford the product 17 as a solid (25 mg, 71% yield). H NMR (DMSO-d6) δ 11.91 (s, 1H), 8.03 (s, 1H), 7.67-7.75 (m, 3H), 7.41-7.44 (m, 2H), 7.27-7.32 (m, 2H), 7.19-7.21 (m, 1H),
Example 2
(R)—N-hydroxy-6-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)heptanamide (Compound 21)

Step 2a. (R)—Ethyl 6-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)hexanoate (Compound 407-21)

[0171] To a mixture of compound 406 (330 mg, 1.0 mmol) and K₂CO₃ (210 mg, 1.5 mmol) in dimethylformamide (2.0 mL) was added ethyl 6-bromohexanoate (223 mg, 1.0 mmol) and the mixture was stirred at 40°C for 20 hours. 5 mL of water was added and the mixture was extracted with ethyl acetate (25 mL×4), dried and concentrated to give a residue which was purified by column chromatography to afford the product 407-21 as a white solid (250 mg, 53% yield). ¹H NMR (DMSO-d₆) δ 11.87 (s, 1H), 8.01 (s, 1H), 7.66-7.69 (m, 3H), 7.39-7.42 (m, 2H), 7.25-7.30 (m, 2H), 7.17-7.19 (m, 1H), 6.92-6.99 (m, 2H), 5.46-5.48 (m, 1H), 3.95-4.07 (m, 4H), 2.29 (t, J=7.2 Hz, 2H), 1.68-1.73 (m, 2H), 1.38-1.60 (m, 8H), 1.15 (t, J=7.2 Hz, 3H). LC-MS: 473 (M+1).

Step 2b. (R)—N-Hydroxy-6-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)hexanoate (Compound 21)

[0172] Preparation of the solution of hydroxylamine in methanol: hydroxylamine hydrochloride (4.67 g, 67 mmol) was dissolved in methanol (24 mL) made to solution A. Potassium hydroxide (5.61 g, 100 mmol) was dissolved in methanol (14 mL) made to solution B. The solution A was cooled to 0°C, and solution B was added into solution A with dropwise. The mixture was stirred for 30 minutes at 0°C, and was allowed to stand at low temperature for some time. The precipitate was isolated to afford solution of hydroxylamine in methanol.

[0173] To a flask containing compound 407-21 (220 mg, 0.466 mmol) was added above solution of hydroxylamine in methanol (3.0 mL). The mixture was stirred at room temperature for 2.0 h. Then it was adjusted to pH 7 using concentrated HCl. The mixture was concentrated to give a residue which was purified by column chromatography to afford the product 21 as a white solid (130 mg, 61% yield). ¹H NMR (DMSO-d₆) δ 11.87 (s, 1H), 10.52 (s, 1H), 8.64 (s, 1H), 8.00 (s, 1H), 7.66-7.69 (m, 3H), 7.39-7.41 (m, 2H), 7.25-7.30 (m, 2H), 7.16-7.19 (m, 1H), 6.92-6.99 (m, 2H), 5.46-5.48 (m, 1H), 3.97 (t, J=6.6 Hz, 2H), 1.95 (t, J=7.2 Hz, 2H), 1.67-1.72 (m, 2H), 1.20-1.39 (m, 8H). LC-MS: 460 (M+1).

Example 3
(R)—N-hydroxy-7-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)heptanamide (Compound 22)

Step 3a. (R)—Ethyl 7-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)heptanoate (Compound 407-22)

[0174] To a mixture of compound 406 (330 mg, 1.0 mmol) and K₂CO₃ (210 mg, 1.5 mmol) in dimethylformamide (2.0 mL) was added ethyl 7-bromohexanoate (237 mg, 1.0 mmol) and the mixture was stirred at 40°C for 20 h. 5 mL of water was added and the mixture was extracted with ethyl acetate (25 mL×4), dried and concentrated to give a residue which was purified by column chromatography to afford the product 407-22 as a white solid (150 mg, 31% yield). ¹H NMR (DMSO-d₆) δ 11.87 (s, 1H), 8.01 (s, 1H), 7.66-7.69 (m, 3H), 7.41 (d, J=7.5 Hz, 2H), 7.25-7.30 (m, 2H), 7.17-7.19 (m, 1H), 6.92-6.99 (m, 2H), 5.46-5.48 (m, 1H), 3.95-4.06 (m, 4H), 2.24-2.29 (t, J=7.2 Hz, 2H), 1.67-1.71 (m, 2H), 1.31-1.55 (m, 10H), 1.15 (t, J=7.2 Hz, 3H). LC-MS: 487 (M+1).

Step 3b. (R)—N-Hydroxy-7-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)heptanamide (Compound 22)

[0175] Preparation of the solution of hydroxylamine in methanol: hydroxylamine hydrochloride (4.67 g, 67 mmol) was dissolved in methanol (24 mL) made to solution A. Potassium hydroxide (5.61 g, 100 mmol) was dissolved in methanol (14 mL) made to solution B. The solution A was cooled to 0°C, and solution B was added into solution A dropwise. The mixture was stirred for 30 minutes at 0°C, and was allowed to stand at low temperature for some time. The precipitate was isolated to afford the solution of hydroxylamine in methanol.

[0176] To a flask containing compound 407-22 (120 mg, 0.247 mmol) was added above solution of hydroxylamine in methanol (3.0 mL). The mixture was stirred at room temperature for 2 h. Then it was adjusted to pH 7 using concentrated HCl. The mixture was concentrated to give a residue which was purified by column chromatography to afford the product 22 as a white solid (90 mg, 77% yield). ¹H NMR (DMSO-d₆) δ 11.87 (s, 1H), 10.30 (s, 1H), 8.62 (s, 1H), 8.00 (s, 1H), 7.66-7.69 (m, 3H), 7.59-7.42 (m, 2H), 7.25-7.30 (m, 2H), 7.16-7.19 (m, 1H), 6.91-6.99 (m, 2H), 5.48-5.49 (m, 1H), 3.97 (t, J=6.6 Hz, 2H), 1.93 (t, J=6.9 Hz, 2H), 1.67-1.72 (m, 2H), 1.20-1.51 (m, 10H). LC-MS: 474 (M+1).

Example 4
(R)—N-Hydroxy-2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido (Compound 1)

Step 4a. Ethyl 3-amino-3-aminopropanoate hydrochloride (Compound 104)

[0177] To anhydrous ethanol (460 g, 10.0 mol) at −30°C was bubbled in anhydrous hydrogen chloride until the total weight of 821 g of HCl/EtOH solution (44% (w/w) was obtained.

[0178] Ethyl cyanoacetate (452 g) was added into the HCl/EtOH solution (292 g), the mixture was cooled to iced-salt bath temperature and stirred for 1.0 h. The reaction was warmed to room temperature and stood overnight. A white precipitate of 102 was obtained and this mixture was used directly in the next step.

[0179] The obtained mixture was added to a mixture of ether and a solution of K₂CO₃ (828 g) in water (2500 mL). The ether layer was separated, dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to give compound 103 (445 g) as a colorless oil.

[0180] A mixture of compound 103 (445 g) and ammonium chloride (149.5 g) in ethanol (1500 mL) was heated to reflux for 8 h. The solid was isolated and the filtrate was concentrated. The residue was washed with ether and acetone to give product 104 (220 g, 33% total yield in three steps). LCMS:
131 [M+1]+. 1H NMR (DMSO-d6): δ 1.22 (t, J=6.9 Hz, 3H), 3.68 (s, 2H), 4.16 (q, J=6.9 Hz, 2H), 9.04 (s, 2H), 9.32 (s, 2H).

Step 4b. Methyl 4-(2-bromoacetyl)benzoate (compound 106)

[0811] Methyl4-acetylbenzoate 105 (8.91 g, 50 mmol) was suspended in acetic acid (80 mL) and the mixture was stirred until a clear solution was reached. Then bromine (8.39 g, 52 mmol) was added dropwise to the mixture. The mixture was stirred at room temperature until the strong orange color disappeared. The solution was cooled to 0°C and the solid was collected and washed with 50% aqueous methanol, dried to give the title compound 106 (9.9 g, 77%). LCMS: 257 [M+1]+; 1H NMR (CDCl3): δ: 3.96 (s, 3H), 4.47 (s, 2H), 8.03 (t, 1H), 8.06 (t, 1H), 8.14 (t, 1H), 8.16 (t, 1H).

Step 4c. Ethyl 5-(4-(methoxycarbonyl)phenyl)-2-amino-1H-pyrrole-3-carboxylate (Compound 107)

[0812] Sodium (1.38 g, 60 mmol) was added to ethanol (150 mL) and stirred until the sodium was dissolved. The reaction was cooled to 0°C and a solution of ethyl 2-aminooctadehydrochloride (10.0 g, 0.06 mol) was added and stirred for 30 min. Methyl 4-(2-bromoacetyl)benzoate 106 (7.71 g, 0.03 mol) was then added. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and the residue was dissolved with ethyl acetate, filtered and the filtrate was washed with water. The aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over MgSO4, and filtered. The filtrate was concentrated and the residue was purified by column chromatography to give the compound 107 (7.38 g, 85.3%). LCMS: 289 [M+1]+; 1H NMR (DMSO-d6): δ: 1.25 (t, J=6.9 Hz, 3H), 3.82 (s, 3H), 4.14 (q, J=6.9 Hz, 2H), 5.81 (s, 2H), 6.71 (s, 1H), 7.61 (d, J=8.7 Hz, 2H), 7.84 (d, J=8.7 Hz, 2H), 10.94 (s, 1H).

Step 4d. Methyl 4-(4-hydroxy-7H-pyrrole[2,3-d]pyrimidin-6-yl)benzoate (Compound 108)

[0813] A mixture of 107 (7.0 g, 24.3 mmol), formic acid (12 mL) and formamide (50 mL) in DMF (24 mL) was heated at 150°C for 16 hours. The reaction mixture was cooled and diluted with isopropylamine and the precipitate was isolated, washed with isopropylamine and hexane to give the title compound 108 (4.1 g, 62.7%). LCMS: 270 [M+1]+; 1H NMR (DMSO-d6): δ: 2.30 (s, 3H), 6.84 (s, 1H), 7.19 (d, J=8.1 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H), 7.84 (s, 1H), 11.80 (s, 1H), 12.24 (s, 1H).

Step 4e. Methyl 4-(4-chloro-7H-pyrrole[2,3-d]pyrimidin-6-yl)benzoate (Compound 109)

[0814] A mixture of compound 108 (4.1 g, 15.2 mmol) and phosphonyl trichloride (30 mL) was reacted at reflux for 3 hours. The excessive phosphonyl trichloride was removed under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with aqueous NaHCO3 solution, brine, dried over MgSO4, filtered and evaporated to give crude product 109 (5.27 g); LCMS: 288 [M+1]+; 1H NMR (DMSO-d6): δ: 2.34 (s, 3H), 7.02 (s, 1H), 7.31 (d, J=8.1 Hz, 2H), 7.88 (d, J=8.1 Hz, 2H), 8.55 (s, 1H), 12.94 (s, 1H).

Step 4f. Methyl 4-((R)-1-phenylethylamino)-7H-pyrrole[2,3-d]pyrimidin-6-yl)benzoate (Compound 110)

[0815] To a suspension of compound 109 (8.4 g, 29.0 mmol) in n-butanol (100 mL) was added (R)-N-phenethylamine (4.5 g, 37 mmol). The mixture was heated at reflux overnight. The reaction mixture was cooled with ice-bath and the precipitate was isolated and washed with n-butanol and ethyl acetate, dried to give the title compound 110 (7.7 g, 71.3%). LCMS: 373 [M+1]+; 1H NMR (DMSO-d6): δ: 1.53 (d, J=6.9 Hz, 3H), 3.87 (s, 3H), 5.51 (s, 1H), 7.20 (d, J=7.2 Hz, 1H), 7.31 (t, J=7.2 Hz, 3H), 7.42 (d, J=7.2 Hz, 2H), 7.93 (t, J=8.4 Hz, 3H), 8.00 (d, J=8.4 Hz, 2H), 8.09 (s, 1H), 12.20 (s, 1H).

Step 4g. (4-((R)-1-phenylethylamino)-7H-pyrrole[2,3-d]pyrimidin-6-yl)phenylmethanol (Compound 111)

[0816] To a suspension of compound 110 (6.15 g, 16.5 mmol) in anhydrous THF (400 mL) was added LiAlH4 (1.88 g, 0.045 mol) in portions. The resulting mixture was heated at reflux for 30 minutes. The mixture was cooled to room temperature and H2O (1.88 mL) was added and followed by addition of 15% aqueous NaOH (1.88 mL) and H2O (5.64 mL). The precipitate was removed by filtration and the filtrate was concentrated. The residue was suspended in water and the precipitate was collected and dried to give the title compound III (4.28 g, 75.3%). LCMS: 345 [M+1]+; 1H NMR (DMSO-d6): δ: 1.54 (d, J=7.2 Hz, 3H), 4.53 (d, J=6.0 Hz, 2H), 5.20 (t, J=6.0 Hz, 1H), 5.50 (m, 1H), 7.08 (s, 1H), 7.20 (t, J=7.5 Hz, 1H), 7.30 (t, J=7.5 Hz, 2H), 7.40 (t, J=8.1 Hz, 4H), 7.76 (t, J=8.4 Hz, 3H), 8.05 (s, 1H), 11.99 (s, 1H).

Step 4h. 6-(4-Chloromethyl)phenyl)-N—(—(R)-1-phenylethyl)-7H-pyrrole[2,3-d]pyrimidin-4-amine (Compound 112)

[0817] To a solution of SOCl2 (8.85 g, 74.0 mmol) in toluene (50 mL) at 0°C, was added compound III in portions. The mixture was warmed to 0°C and stirred for 2 hours. The reaction mixture was filtered and the solid was washed with toluene and ether to give crude product. The crude product was suspended in water and treated with saturated aqueous NaHCO3, until pH=7. The solid was isolated and washed with water, dried to give the title compound 112 (1.8 g, 67.0%). LCMS: 363 [M+1]+; 1H NMR (DMSO-d6): δ: 1.54 (d, J=6.9 Hz, 3H), 4.79 (s, 2H), 5.50 (m, 1H), 7.14 (s, 1H), 7.20 (d, J=7.2 Hz, 1H), 7.30 (t, J=7.2 Hz, 2H), 7.42 (d, J=6.9 Hz, 2H), 7.49 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.7 Hz, 2H), 7.82 (d, J=8.4 Hz, 1H), 8.07 (s, 1H), 12.06 (s, 1H).

Step 4i. (R)-Ethyl 2-((R)-1-phenylethylamino)-7H-pyrrole[2,3-d]pyrimidin-6-yl)benzylamino) acetate (Compound 113-1)

[0818] To a mixture of DMF (60 mL), MeOH (30 mL) and KOH (148 mg, 8.0 mmol) was added ethyl 2-aminoacetate hydrochloride (1.11 g, 8.0 mmol). The resulting mixture was stirred at room temperature for 10 minutes. MeOH was removed at 40°C under reduced pressure and compound 112 (724 mg, 2.0 mmol) was added. The resulting mixture was stirred at room temperature overnight. DMF was removed.
under reduced pressure and the residue was suspended in water. The resulting solid was collected and dried to give product 113-1 (285 mg, 33%). LCMS: 430 [M+1]⁺.

Step 4j. (R)—N-hydroxy-2-(4-(4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)propanamide (Compound 11)

[0189] A mixture of compound 113-1 (285 mg, 0.66 mmol) and NH₄OH/MeOH (5 mL, 8.85 mmol) was stirred at room temperature for 0.5 h. The reaction mixture was neutralized with AcOH and concentrated. The residue was suspended in water and resulting precipitate was isolated and dried to give crude product. This product was purified by preparative HPLC to give compound 1 as a pale yellow solid (220 mg, 80%). LCMS: 417 [M+1]⁺; ¹H NMR (DMSO-d₆): δ 1.52 (d, J=6.3 Hz, 3H), 3.02 (s, 2H), 3.67 (s, 2H), 5.47 (m, 1H), 7.06 (s, 1H), 7.17 (t, J=6.9 Hz, 1H), 7.28 (m, 2H), 7.39 (m, 4H), 7.70 (m, J=7.8 Hz, 2H), 7.78 (d, J=8.1 Hz, 1H) 8.03 (s, 1H), 8.80 (s, 1H), 10.41 (s, 1H), 11.99 (s, 1H).

Example 5

Preparation of (R)—N-hydroxy-3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)propanamide (Compound 2)

Step 5a. (R)-Ethyl 3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)propanoate (Compound 2)

[0190] The title compound 113-2 was prepared (200 mg, 53%) from compound 112 (200.0 mg, 0.8 mmol) and ethyl 3-amino-propanoic hydrochloride (368 mg, 2.4 mmol) using a procedure similar to that described for compound 113-1 (Example 4): LCMS: 444 [M+1]⁺.

Step 5b. (R)—N-hydroxy-3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)propanamide (Compound 2)

[0191] The title compound 2 was prepared as a pale yellow solid (45 mg, 24%) from compound 113-2 (190.0 mg, 0.43 mmol) and NH₂OH/MeOH (2 mL, 3.43 mmol) using a procedure similar to that described for compound 1 (Example 4): LCMS: 431 [M+1]⁺; ¹H NMR (DMSO-d₆): δ 1.52 (d, J=6.9 Hz, 3H), 2.14 (t, J=7.2 Hz, 2H), 2.70 (t, J=7.2 Hz, 2H), 3.69 (s, 2H), 5.50 (m, 1H), 7.07 (s, 1H), 7.19 (t, J=6.9 Hz, 1H), 7.30 (t, J=7.2 Hz, 2H), 7.36 (d, J=7.8 Hz, 2H), 7.42 (d, J=7.8 Hz, 2H), 7.74 (m, 3H), 8.05 (s, 1H), 11.97 (s, 1H).

Example 6

(R)—N-Hydroxy-2-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazine-1-ylpropanamide (Compound 11)

Step 6a. (R)—N-(1-Phenylethyl)-6-(4-(piperazin-1-ylmethyl)phenyl)-7H-pyrrrolo[2,3-d]pyrimidin-4-amine (Compound 301)

[0192] A mixture of compound 112 (0.1 g, 0.27 mmol) and piperazine (0.21 g, 2.7 mmol) in DMF (20 mL) was stirred at 20°C for 1.5 hours. The solvent was removed under reduced pressure and the residue was washed with water, dried and purified by HPLC to obtain the title compound 301 as a yellow solid (0.10 g, 87.8%): LCMS: 413 [M+1]⁺.

Step 6b. (R)-Ethyl 2-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-3-yl)benzyl)piperazine-1-ylacetate (Compound 302-11)

[0193] A mixture of compound 301 (0.25 g, 0.61 mmol), ethyl 2-bromoacetate (0.11 g, 0.66 mmol), triethylamine (0.25 g, 2.44 mmol) in DMF (10 mL) was stirred at 25-30°C overnight. The solvent was evaporated under reduced pressure to give crude residue 302-11 (0.30 g, LCMS: 499 [M+1]⁺) which was used in the next step directly without further purification.

Step 6c. (R)—N-Hydroxy-2-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazine-1-ylacetamide (Compound 11)

[0194] To a solution of hydroxylamine in methanol (4.0 mL, 7.1 mmol) was added compound 302-11 (0.30 g, 0.62 mmol). The reaction mixture was stirred at 25°C for 20 minutes. The reaction was monitored by TLC. The mixture was neutralized with acetic acid and concentrated under reduce pressure. The residue was purified by preparative HPLC to give the title compound 11 as a white solid (60 mg, 21%): LCMS: 486 [M+1]⁺; ¹H NMR (DMSO-d₆): δ 1.32 (d, J=6.9 Hz, 3H), 2.43 (m, 8H), 2.83 (s, 2H), 3.44 (s, 2H), 5.47 (m, 1H), 7.05 (s, 1H), 7.19 (m, 1H), 7.29 (m, 5H), 7.40 (d, J=7.2 Hz, 3H), 7.71 (d, J=8.1 Hz, 2H), 7.76 (d, J=8.1 Hz, 1H), 8.02 (s, 1H), 11.96 (s, 1H).

Example 7

(R)—N-Hydroxy-3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazine-1-ylpropanamide (Compound 12)

Step 7a. (R)-Methyl 3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazine-1-ylpropanoate (compound 302-12)

[0195] The title compound 302-12 was prepared (0.31 g) from compound 301 (0.44 g, 1.07 mmol), methyl 3-bromopropanoate (0.20 g, 1.17 mmol) and triethylamine (0.43 g, 4.25 mmol) in DMF (9 mL) using a procedure similar to that described for compound 302-11 (Example 6): LCMS: 499 [M+1]⁺.

Step 7b. (R)—N-Hydroxy-3-(4-(4-(1-phenethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazine-1-ylpropanamide (Compound 12)

[0196] The title compound 12 was prepared as a white solid (80 mg, 26%) from compound 302-12 (0.31 g, 0.62 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 500 [M+1]⁺; ¹H NMR (DMSO-d₆): δ 1.62 (d, J=7.2 Hz, 3H), 2.29 (t, J=7.2 Hz, 2H), 2.54 (m, 8H), 2.67 (t, J=7.2 Hz, 3H), 3.56 (s, 2H), 5.47 (m, 1H), 7.00 (s, 1H),
7.19 (m, 1H), 7.29 (m, 5H), 7.40 (d, J=7.2 Hz, 3H), 7.71 (d, J=8.1 Hz, 2H), 7.76 (d, J=8.1 Hz, 1H), 8.02 (s, 1H), 11.96 (s, 1H).

**Example 8**

(R)—N-Hydroxy-4-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)butanamide (Compound 13)

Step 8a. (R)—Ethyl 4-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)butanoate (Compound 302-13)

**[0197]** The title compound 302-13 was prepared (0.39 g) from compound 301 (0.30 g, 0.74 mmol), ethyl 4-bromobutanonoate (0.28 g, 0.82 mmol), triethylamine (0.29 g, 2.9 mmol) and DMF (9.5 mL) using a procedure similar to that described for compound 302-11 (Example 6): LCMS: 527 [M+H]+.

Step 8b. (R)—N-Hydroxy-4-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)butanamide (Compound 13)

**[0198]** The title compound 13 was prepared as a white solid (20 mg, 5%) from compound 302-13 (0.39 g, 0.74 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 514 [M+H]+; 1H NMR (DMSO-d6): δ1.15 (m, 2H), 1.34 (m, 2H), 1.41 (m, 2H), 1.51 (d, J=6.9 Hz, 3H), 1.91 (t, J=6.9 Hz, 2H), 2.20 (t, J=6.9 Hz, 2H) 2.35 (m, 8H), 3.34 (s, 2H), 5.48 (m, 1H), 7.68 (s, 1H), 7.17 (m, 1H), 7.29 (m, 1H), 7.43 (d, J=6.9 Hz, 3H), 7.74 (d, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 1H), 8.05 (s, 1H), 12.00 (s, 1H).

**Example 9**

(R)—N-Hydroxy-5-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)pentanamide (Compound 14)

Step 9a. (R)—Methyl 5-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)pentanate (Compound 302-14)

**[0199]** The title compound 302-14 was prepared (0.40 g) from compound 301 (0.31 g, 0.76 mmol), methyl 5-bromopentanate (0.178 g, 0.91 mmol), triethylamine (0.31 g, 3.1 mmol) and DMF (10 mL) using a procedure similar to that described for compound 302-11 (Example 6): LCMS: 527 [M+H]+.

Step 9b. (R)—N-Hydroxy-5-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)pentanamide (Compound 14)

**[0200]** The title compound 14 was prepared as a white solid (30 mg, 7%) from compound 302-14 (0.40 g, 0.76 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 528 [M+H]+; 1H NMR (DMSO-d6): δ1.29 (m, 2H), 1.38 (m, 2H), 1.46 (d, J=7.2 Hz, 3H), 1.86 (t, J=7.2 Hz, 2H), 2.16 (t, J=3.9 Hz, 2H) 2.30 (m, 8H), 3.39 (s, 2H), 5.43 (m, 1H), 7.0 (s, 1H), 7.12 (m, 1H), 7.26 (m, 5H), 7.35 (d, J=7.5 Hz, 3H), 7.76 (d, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 1H), 7.98 (s, 1H).

**Example 10**

(R)—N-Hydroxy-6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)hexanamide (Compound 15)

Step 10a. (R)—Ethyl 6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)hexanoate (Compound 302-15)

**[0201]** The title compound 302-15 was prepared (0.41 g) from compound 301 (0.30 g, 0.73 mmol), ethyl 6-bromohexananoate (0.21 g, 0.87 mmol), triethylamine (0.29 g, 2.9 mmol) and DMF (8 mL) using a procedure similar to that described for compound 302-11 (Example 6): LCMS: 555 [M+H]+.

Step 10b. (R)—N-Hydroxy-6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)hexanamide (Compound 15)

**[0202]** The title compound 15 was prepared as a white solid (80 mg, 20%) from compound 302-15 (0.41 g, 0.74 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 542 [M+H]+; 1H NMR (DMSO-d6): δ1.15 (m, 2H), 1.34 (m, 2H), 1.41 (m, 2H), 1.51 (d, J=6.9 Hz, 3H), 1.91 (t, J=6.9 Hz, 2H), 2.20 (t, J=6.9 Hz, 2H) 2.35 (m, 8H), 3.34 (s, 2H), 5.48 (m, 1H), 7.68 (s, 1H), 7.18 (m, 1H), 7.29 (m, 4H), 7.41 (d, J=7.2 Hz, 2H), 7.72 (d, J=8.1 Hz, 2H), 7.79 (d, J=8.4 Hz, 1H), 8.03 (s, 1H), 8.65 (s, 1H), 10.30 (s, 1H), 11.98 (s, 1H).

**Example 11**

(R)—N-Hydroxy-7-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)heptanamide (Compound 16)

Step 11a. (R)—Ethyl 7-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)pentanate (Compound 302-16)

**[0203]** The title compound 302-16 was prepared (0.13 g, 23%) from compound 301 (0.41 g, 1.0 mmol), ethyl 7-bromohexanoate (0.237 g, 1 mmol), triethylamine (0.40 g, 4.0 mmol) and DMF (6 mL) using a procedure similar to that described for compound 302-11 (Example 6): LCMS: 569 [M+H]+.

Step 11b. (R)—N-Hydroxy-7-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-yl)benzyl)piperazin-1-yl)heptanamide (Compound 16)

**[0204]** The title compound 16 was prepared as a brown solid (84 mg, 66%) from compound 302-16 (0.13 g, 0.23 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 556 [M+H]+; 1H NMR (DMSO-d6): δ1.23 (m, 4H), 1.46 (m, 4H), 1.51 (d, J=7.2 Hz, 3H), 1.92 (t, J=7.8 Hz, 2H), 2.50-2.80 (m, 8H), 3.56 (s, 1H), 5.48 (m, 1H), 7.09 (s, 1H), 7.18 (m, 1H), 7.26 (m, 2H), 7.40
Example 12

(R)-N-Hydroxy-4-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propanamide (Compound 19)

Step 12a. (R)-Methyl-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)butanoate (Compound 407-19)

[0205] To a mixture of compound 406 (250 mg, 0.75 mmol) and K$_2$CO$_3$ (160 mg, 1.2 mmol) in N,N-dimethylformamide (1.5 mL) was added methyl 4-bromobutrate (130 mg, 0.75 mmol) and the resulting mixture was stirred at 40°C for 20 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (25 mL x 4), dried and concentrated. The residue was purified by column chromatography to afford the product 407-19 as a white solid (202 mg, 63% yield): LC-MS: 431 (M+1); H NMR (DMSO-d$_6$): δ 1.49 (d, J=6.6 Hz, 3H), 1.90–1.93 (m, 2H), 2.11 (t, J=7.2 Hz, 2H), 3.60 (s, 3H), 4.02 (t, J=6.0 Hz, 2H), 5.43-5.48 (m, 1H), 6.92-6.98 (m, 2H), 7.16-7.18 (m, 1H), 7.24-7.29 (m, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.65-7.71 (m, 3H), 8.00 (s, 1H), 11.87 (s, 1H).

Step 12b. (R)-N-Hydroxy-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propionamide (Compound 19)

[0206] To a flask containing compound 407-19 (180 mg, 0.45 mmol) was added the solution of hydroxylamine in methanol (2.0 mL). The mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with conc. HCl and concentrated. The residue was purified by column chromatography to afford the product 19 as a white solid (60 mg, 34% yield): LC-MS: 452 (M+1); H NMR (DMSO-d$_6$): δ 1.49 (d, J=6.6 Hz, 3H), 1.89–1.93 (m, 2H), 2.10 (t, J=7.2 Hz, 2H), 3.97 (t, J=6.0 Hz, 2H), 5.43-5.48 (m, 1H), 6.92-6.98 (m, 2H), 7.16-7.18 (m, 1H), 7.24-7.29 (m, 2H), 7.38-7.41 (m, J=8.4 Hz, 2H), 7.65-7.71 (m, 3H), 7.99 (s, 1H), 8.70 (s, 1H), 10.41 (s, 1H), 11.88 (s, 1H).

Example 13

(R)-N-Hydroxy-5-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)pentanamide (Compound 20)

Step 13a. (R)-Methyl-5-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)pentanoate (Compound 407-20)

[0207] The title compound 407-20 was prepared as a white solid (150 mg, 87%) from compound 406 (150 mg, 0.39 mmol), K$_2$CO$_3$ (110 mg, 0.8 mmol), methyl 5-bromovalerate (76 mg, 0.39 mmol) using a procedure similar to that described for compound 407-19 (Example 12): LC-MS: 445 (M+1); H NMR (DMSO-d$_6$): δ 1.47-1.54 (m, 5H), 1.88-1.94 (m, 2H), 2.36 (t, J=7.5 Hz, 2H), 3.58 (s, 3H), 3.80-4.33 (m, 2H), 5.46-5.50 (m, 1H), 6.91-6.98 (m, 2H), 7.16-7.18 (m, 1H), 7.24-7.30 (m, 2H), 7.40 (d, J=7.5 Hz, 2H), 7.65-7.68 (m, 3H), 8.00 (s, 1H), 11.87 (s, 1H).

Step 13b. (R)-N-Hydroxy-5-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)pentanamide (Compound 20)

[0208] The title compound 20 was prepared as a white solid (110 mg, 73%) from compound 407-20 (150 mg, 0.35 mmol) using a procedure similar to that described for compound 19 (Example 12): LC-MS: 446 (M+1); H NMR (DMSO-d$_6$): δ 1.50 (d, J=7.2 Hz, 3H), 1.65-1.66 (m, 4H), 1.98-2.02 (m, 2H), 3.97 (m, 2H), 5.44-5.49 (m, 1H), 6.93-6.99 (m, 2H), 7.16-7.18 (m, 1H), 7.25-7.30 (m, 2H), 7.39-7.41 (d, J=8.4 Hz, 2H), 7.66-7.71 (m, 3H), 8.00 (s, 1H), 8.70 (s, 1H), 10.42 (s, 1H), 11.87 (s, 1H).

Example 14

(R)-N'-Hydroxy-N'-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)succinamide (Compound 24)

Step 14a. Ethyl 2-amino-5-(4-nitrophenyl)-1H-pyrrole-3-carboxylate (Compound 502)

[0209] Under a nitrogen atmosphere, compound 104 (16.7 g, 100 mmol) was introduced into 25 mL of ethanol at 0.75°C followed by sodium ethanolate (6.8 g, 100 mmol). The yellow suspension was stirred for 20 minutes and compound 501 (12.2 g, 50 mmol) was added. The resulting mixture was stirred for 24 hours at room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO$_4$ and evaporated to afford crude product 502 (12.1 g, 79.5%). LC-MS: 276 (M+1); H NMR (DMSO-d$_6$): δ 1.26 (t, J=7.2 Hz, 3H), 1.70-1.72 (m, 2H), 5.98 (s, 1H), 6.91 (s, 1H), 7.68 (d, J=9.0 Hz, 2H), 8.13 (d, J=9.0 Hz, 2H), 110.1 (s, 1H).

Step 14b. 6-(4-Nitrophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Compound 503)

[0210] A mixture of 502 (5.0 g, 18.2 mmol), formamide (36 mL) and formic acid (6 mL) in DMF (10 mL) were stirred at 150°C for 22 hours. The mixture was cooled to room temperature and diluted with water. The resulting precipitate was filtered and washed with water, isopropanol, ether and dried to obtain a gray solid 503 (3.24 g, 69.4%). LC-MS: 257 (M+1); H NMR (DMSO-d$_6$): δ 6.72 (s, 1H), 7.95 (s, 1H), 8.11 (d, J=9.0 Hz, 2H), 8.26 (d, J=9.0 Hz, 2H), 11.98 (s, 1H), 12.67 (s, 1H).

Step 14c. 4-Chloro-6-(4-nitrophenyl)-7H-pyrrolo[2,3-d]pyrimidine (Compound 504)

[0211] A mixture of 503 (0.52 g, 2.03 mmol) and phosphorus oxychloride (10 mL) were refluxed for 3 hours. The dark brown suspension was concentrated to remove the phosphorus oxychloride. The residue was diluted with ethyl acetate and the organic layer was washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$ and evaporated to give the prod-
uct 504 as a yellow solid (0.13 g, 22.2%). LC-MS: 275 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(87.42\) (s, 1H), 8.28-8.37 (m, 4H), 8.67 (s, 1H), 13.31 (s, 1H).

Step 14d. (R)-6-(4-Nitrophenyl)-N-(1-phenethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 505)

**[0212]** Compound 504 (5.53 g, 20.1 mmol) was suspended in n-butanol (110 mL) and treated with (R)-phenethylamine (4.9 g, 40.3 mmol). The mixture was heated at 145°C for 24 h. The reaction mixture was cooled in an ice bath and the solid was filtered and washed with cold n-butanol and ether to obtain a black product 505 (4.2 g, 58.2%). LC-MS: 360 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(81.52\) (d, \(J=6.6\) Hz, 3H), 5.52 (m, 1H), 7.21-7.49 (m, 6H), 8.00-8.32 (m, 6H), 13.56 (s, 1H).

Step 14e. (R)-6-(4-Aminophenyl)-N-(1-phenethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 506)

**[0213]** A mixture of compound 505 (5.44 g, 15.14 mmol), iron dust (8.48 g, 0.15 mol) and concentrated HCl (1 mL) in ethanol (120 mL) and water (12 mL) was refluxed for 2 hours. The mixture was adjusted to pH=12 with aqueous NaOH and iron dust was removed by filtration. The filtrate was concentrated to yield a residue which was purified by column chromatography to give product 506 as a yellow solid (1.48 g, 29.7%). LC-MS: 330 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(80.49\) (d, \(J=6.9\) Hz, 3H), 1.79 (t, \(J=7.5\) Hz, 2H), \(2.00\) (t, \(J=7.2\) Hz, 2H), \(2.31\) (t, \(J=7.2\) Hz, 2H), 5.46 (m, 1H), 6.98 (s, 1H), 7.14-7.41 (m, 5H), 7.61-7.75 (m, 5H), 8.01 (s, 1H), 8.68 (s, 1H), 9.87 (s, 1H), 10.37 (s, 1H), 11.90 (s, 1H).

Step 14f. (R)-Methyl 4-oxo-4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenylbutanoate (Compound 507-24)

**[0214]** A solution of succinic acid monomethyl ester (401.6 mg, 3.04 mmol) in SOCl\(_2\) (20 mL) was heated at 80°C for 4 h. The mixture was allowed to cool and the solvent was removed by evaporation. This mixture was then added dropwise to a suspension of compound 506 (0.5 g, 1.52 mmol) in CH\(_2\)Cl\(_2\) (50 mL) and triethylamine (0.86 mL, 6.08 mmol) at 0°C. The mixture was stirred for 2 hours at 0°C and was diluted with CH\(_2\)Cl\(_2\) (150 mL) and washed with water (100 mLx3), dried over MgSO\(_4\). The organic solvent was removed to give crude product 507-24 as a yellow solid (0.7 g) that was used in the next step directly without further purification. LC-MS: 444 (M+1).

Step 14g. (R) — N\(^1\)-Hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenylsuccinamide (Compound 24)

**[0215]** A mixture of 507-24 and saturated solution of hydroxylamine in methanol (1.77 mol/L, 5.15 mL) was stirred for 2.5 hours at room temperature. The mixture was adjusted to pH=7-8 with acetic acid and solvent was removed by evaporation. Water was added to the mixture and the precipitate was filtered and purified to give product 24 as a yellow solid (0.12 g, 17.8% in two steps). LC-MS: 445 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(81.50\) (d, \(J=6.6\) Hz, 3H), 2.29 (t, \(J=7.5\) Hz, 2H), 2.57 (t, \(J=7.2\) Hz, 2H), 5.47 (m, 1H), 6.99 (s, 1H), 7.17-7.42 (m, 5H), 7.65-7.76 (m, 5H), 8.02 (s, 1H), 8.72 (s, 1H), 10.06 (s, 1H), 10.43 (s, 1H), 11.91 (s, 1H).

Example 15

(R)—N\(^1\)-Hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenylglutaramide (Compound 25)

**[0216]** The title compound 507-25 was prepared as a red viscous liquid (0.8 g) from compound 506 (0.5 g, 1.52 mmol) and glutaric acid monomethyl ester (222.1 mg, 3.04 mmol) using a procedure similar to that described for compound 507-24 (Example 14): LC-MS: 458 (M+1).

Step 15b. (R) — N\(^1\)-Hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenylglutaramide (Compound 25)

**[0217]** The title compound 25 was prepared as a yellow solid (0.22 g, 31.6% yield in two steps) from of hydroxylamine in methanol (1.77 mol/L, 3.44 mL) using a procedure similar to that described for compound 24 (Example 14): LC-MS: 459 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(81.49\) (d, \(J=6.9\) Hz, 3H), 1.79 (t, \(J=7.5\) Hz, 2H), \(2.00\) (t, \(J=7.2\) Hz, 2H), \(2.31\) (t, \(J=7.2\) Hz, 2H), 5.46 (m, 1H), 6.98 (s, 1H), 7.14-7.41 (m, 5H), 7.61-7.75 (m, 5H), 8.01 (s, 1H), 8.68 (s, 1H), 9.87 (s, 1H), 10.37 (s, 1H), 11.90 (s, 1H).

Example 16

(R) — N\(^1\)-Hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyladipamide (Compound 26)

Step 16a. (R)-Methyl 6-oxo-6-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenylhexanoate (Compound 507-26)

**[0218]** The title compound 507-26 was prepared as a yellow solid (0.44 g) from compound 506 (0.25 g, 0.76 mmol) and adipic acid monomethyl ester (243.5 mg, 1.52 mmol) using a procedure similar to that described for compound 507-24 (Example 14): LC-MS: 472 (M+1).

Step 16b. (R) — N\(^1\)-hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyladipamide (Compound 26)

**[0219]** The title compound 26 was prepared as a white solid (0.15 g, 41.8% yield in two steps) from 507-26 (0.31 g, 0.62 mmol) using a procedure similar to that described for compound 24 (Example 14): LC-MS: 473 (M+1), \(^1\)H NMR (DMSO-d\(_6\)) \(81.51\) (m, 7H), 1.95 (t, \(J=6.9\) Hz, 2H), 2.30 (t, \(J=6.6\) Hz, 2H), 5.46 (m, 1H), 6.97 (s, 1H), 7.14-7.41 (m, 5H), 7.61-7.75 (m, 5H), 8.01 (s, 1H), 8.66 (s, 1H), 9.95 (s, 1H), 10.34 (s, 1H), 11.90 (s, 1H).

Example 17

(R)—N\(^1\)-Hydroxy-N\(^4\)-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyloctanamide (Compound 27)

Step 17a. (R)-Methyl 8-oxo-8-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyloctanoate (Compound 507-27)

**[0220]** The title compound 507-27 was prepared as a yellow solid (1.12 g) from compound 506 (0.5 g, 1.52 mmol) and
suberic acid monomethyl ester (571.9 mg, 3.04 mmol) using a procedure similar to that described for compound 507-24 (Example 14): LC-MS: 500 (M+1).

Step 17b. (R)—N\textsuperscript{1}-Hydroxy-N\textsuperscript{4}-[(4-[(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenyl]octanediamide (Compound 27)

[0221] The title compound 27 was prepared as a white solid (0.2 g, 26.3% yield in two steps) from 507-27 using a procedure similar to that described for compound 24 (Example 14). LC-MS: 501 (M+1), \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): δ 1.26–1.58 (m, 1H), 1.89 (t, J=7.2 Hz, 2H), 2.28 (t, J=7.2 Hz, 2H), 5.46 (m, 1H), 6.98 (s, 1H), 7.13–7.41 (m, 5H), 7.61–7.75 (m, 5H), 8.01 (s, 1H), 8.63 (s, 1H), 9.34 (s, 1H), 10.50 (s, 1H), 11.90 (s, 1H).

Example 18

(R)—N-(2-(2-(Hydroxyamino)-2-oxoethylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 28)

Step 18a. (R)—N-(2-Aminoethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 601)

[0222] Compound 110 (2.0 g, 5.37 mmol) in ethane-1,2-diamine (120 mL) was stirred at 70°C for 22 hours. The mixture was concentrated under reducing pressure. The residue was dissolved in 3 mL ethanol and diluted with ether. The resulting precipitate was filtered, dried and yellow solid, 601 (2.0 g, 93.0%). LC-MS: 401 [M+1]⁺, \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): δ 1.54 (d, 3H), 2.53 (t, J=1.8 Hz, 1H), 2.72 (t, J=6.0 Hz, 2H), 3.30 (m, J=6.0 Hz, 2H), 5.51 (m, J=6.6 Hz, J=7.8 Hz, 2H), 7.22 (s, 1H), 7.24 (s, J=4.2 Hz, 1H), 7.31 (d, J=7.2 Hz, 1H), 7.44 (d, J=7.5 Hz, 2H), 7.8 (s, 1H), 7.89 (d, J=7.2 Hz, 2H), 7.93 (s, 2H), 7.96 (s, 1H), 8.09 (s, 1H), 8.49 (t, J=5.7 Hz, 1H).

Step 18b. (R)-ethyl 2-(2-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide)ethylenamineacetate (Compound 602-28)

[0223] A solution of 601 (1.0 g, 2.5 mmol) and ethyl 2-bromoacetate (0.42 g, 2.5 mmol) in N,N-dimethylformamide (25 mL) was stirred at room temperature for 4 hours. The solvent was removed and the residue was purified by silica gel column chromatography to obtain 602-28 (0.79 g, 43.2%). LC-MS: 487 [M+1]⁺.

Step 18c. (R)—N-(2-(2-(Hydroxyamino)-2-oxoethylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 28)

[0224] The mixture of 602-28 (0.423 g, 0.87 mmol) and hydroxyamine in methanol (1.77 mol/L, 4.91 mL) were stirred for 2.5 hours at room temperature. The mixture was adjusted to pH 7–8 with acetic acid and solvent was removed. The resulting mixture was diluted with water, filtered and the solid was purified as compound 28 as a yellow solid (0.09 g, 21.8%): LC-MS: 474 [M+1]⁺, \textsuperscript{1}H NMR (DMSO-d\textsubscript{6},CD\textsubscript{3}OD): δ 1.48 (d, J=6.9 Hz, 3H), 2.60 (t, J=6.0 Hz, 2H), 3.04 (s, 2H), 3.31 (t, 2H), 5.37 (m, 1H), 7.14–7.38 (m, 6H), 7.84 (s, 4H), 7.98 (s, 1H).

Example 19

(R)—N-(2-(3-(Hydroxyamino)-3-oxopropylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 29)

Step 19a. (R)-Methyl 3-(2-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide)ethylamino)propanoate (Compound 602-29)

[0225] The title compound 602-29 was prepared as a solid (0.29 g, 23.4%) from compound 601 (1.0 g, 2.5 mmol) and methyl 3-bromopropionate (0.42 g, 2.5 mmol) in N,N-dimethylformamide (25 mL) using a procedure similar to that described for compound 602-28 (Example 18): LC-MS: 487 [M+1]⁺.

Step 19b. (R)—N-(2-(3-(Hydroxyamino)-3-oxopropylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 29)

[0226] The title compound 29 was prepared as a solid (0.04 g, yield 13.9%) from compound 602-29 (0.29 g, 0.59 mmol) and hydroxyamine in methanol (1.77 mol/L, 6 mL) using a procedure similar to that described for compound 28 (Example 18): LC-MS: 488 [M+1]⁺, \textsuperscript{1}H NMR (DMSO-d\textsubscript{6},D\textsubscript{2}O): δ 1.50 (d, J=6.9 Hz, 3H), 2.15 (d, J=6.3 Hz, J=7.2 Hz, 2H), 2.76 (m, 4H), 3.35 (m, 2H), 5.44 (m, 1H), 7.16 (d, J=6.9 Hz, 2H), 7.27 (t, J=7.5 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H), 7.86 (m, 4H), 8.03 (s, 1H).

Example 20

(R)—N-(2-(6-(Hydroxyamino)-6-oxohexylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (Compound 30)

Step 20a. (R)-Ethyl 2-(2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide)hexanoate (Compound 602-30)

[0227] The title compound 602-30 was prepared as a solid (0.26 g, 24.0%) from compound 601 (0.8 g, 2.0 mmol) and ethyl 6-bromohexanoate (0.446 g, 2.0 mmol) in N,N-dimethylformamide (20 mL) using a procedure similar to that described for compound 602-28 (Example 18): LC-MS: 543 [M+1]⁺.

Step 20b. (R)—N-(2-(6-(Hydroxyamino)-6-oxohexylamino)ethyl)-4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamide (compound 30)

[0228] The title compound 30 was prepared as a yellow solid (0.07 g, 27.6%) from compound 602-30 (0.260 g, 0.48 mmol) and the solution of hydroxyamine in methanol (1.77 mol/L, 6 mL) using a procedure similar to that described for compound 28 (Example 18): LC-MS: 530 [M+1]⁺, \textsuperscript{1}H NMR
Example 21

(R)—N-(2-(7-(Hydroxyamino)-7-oxoheptylaminio)ethyl)-4-(4-(1-phenyl ethyl-amino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido)ethylheptanoate (Compound 31)

Step 21a. (R)—Ethyl 7-(2-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido)ethylheptanoate (Compound 30-21) [0229] The title compound 602-31 was prepared (0.40 g, 19.0%) from compound 601 (1.5 g, 3.75 mmol) and ethyl 7-bromopentanate (0.889 g, 3.75 mmol) in N,N-dimethylformamide (50 mL) using a procedure similar to that described for compound 602-28 (Example 18): LC-MS: 557 [M+H]⁺.

Step 21b. (R)—N-(2-(7-(Hydroxyamino)-7-oxoheptylaminio)ethyl)-4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido)ethylheptanoate (Compound 31) [0230] The title compound 31 was prepared as a yellow solid (0.072 g, 18.7%) from compound 602-31 (0.396 g, 0.71 mmol) and hydroxyamine in methanol (1.77 mol/L, 8 mL) using a procedure similar to that described for compound 30-21 (Example 18): LC-MS: 544 [M+H]⁺, 31 ¹H NMR (DMSO-d₆ + D₂O): δ 1.20 (s, 4H), 1.48 (s, 7H), 1.93 (s, 2H), 2.69 (s, 2H), 2.89 (s, 2H), 3.46 (s, 2H), 5.37 (s, 1H), 7.10–7.50 (m, 6H), 7.85 (s, 4H), 7.99 (s, 1H).

Example 22

Preparation of (R)—N-hydroxy-6-(4-(1-phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)hexanoamide (Compound 32)

Step 22a. (R)—Methyl 6-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido)hexanoate (Compound 113-32) [0231] To a mixed solution of DMF (10 mL) and MeOH (5 mL) was added KOH (160.8 mg, 3.0 mmol) and methyl 6-aminoheptanoate hydrochloride (545.0 mg, 3.0 mmol). The mixture was stirred at room temperature for 10 minutes and MeOH was removed at 40°C under reduced pressure. Compound 112 (363 mg, 1 mmol) was added to the above mixture and was stirred at room temperature overnight. DMF was removed under reduced pressure and the residue was suspended in water. The resulting solid was collected and dried to give product 113-32 (280 mg, 59%). LCMS: 472 [M+H]⁺.

Step 22b. (R)—N-Hydroxy-6-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzamido)hexanoamide (Compound 32) [0232] A mixture of compound 113-32 (280.0 mg, 0.59 mmol) and NH₂OH/MeOH (2.7 mL, 4.75 mmol) was stirred at room temperature for 0.5 hours. The reaction mixture was neutralized with acetic acid and concentrated. The residue was suspended in water and the resulting precipitate was isolated and dried to give crude product that was purified by preparative HPLC to give product 32 as a pale yellow solid (48 mg, 17% yield in two steps): LCMS: 473 [M+H]⁺, 31 ¹H NMR (DMSO-d₆): δ 81.27 (m, 2H), 1.46 (m, 4H), 1.52 (d, J=7.2 Hz, 3H), 1.94 (t, J=7.2 Hz, 2H), 2.59 (t, J=7.2 Hz, 2H), 3.81 (s, 2H), 5.47 (m, 1H), 7.09 (s, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.30 (t, J=7.7 Hz, 2H), 7.41 (d, J=7.7 Hz, 4H), 7.76 (m, 3H), 8.05 (s, 1H), 10.32 (s, 1H), 12.00 (s, 1H).

Example 23

Preparation of (R)—N-hydroxy-7-(4-(1-phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)heptanoamide (Compound 33)

Step 23a. (R)—Methyl 7-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)heptanoate (Compound 113-33) [0233] The title compound 113-33 was prepared (102 mg, 25%) from compound 112 (300 mg, 0.83 mmol) and 7-amino-heptanoate hydrochloride (487 mg, 2.49 mmol) using a procedure similar to that described for compound 113-32 (Example 22): LCMS: 486 [M+H]⁺.

Step 23b. (R)—N-hydroxy-7-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)heptanoamide (Compound 33) [0234] The title compound 33 was prepared as a pale yellow solid (28 mg, 29%) from compound 113-33 (97 mg, 0.2 mmol) and NH₂OH/MeOH (3 mol, 5.31 mmol) using a procedure similar to that described for compound 30-21 (Example 22): LCMS: 487 [M+H]⁺, 1 ¹H NMR (DMSO-d₆): δ 1.24 (m, 2H), 1.43 (m, 6H), 1.52 (d, J=7.2 Hz, 3H), 1.93 (t, J=7.5 Hz, 2H), 1.95 (m, 2H), 3.71 (s, 2H), 5.50 (m, 1H), 7.06 (s, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.30 (t, J=7.2 Hz, 2H), 7.40 (d, J=8.1 Hz, 2H), 7.42 (d, J=7.5 Hz, 2H), 7.71 (t, J=8.1 Hz, 3H), 8.05 (s, 1H), 8.62 (s, 1H), 10.29 (s, 1H), 11.95 (s, 1H).

Example 24

Preparation of (R)—N-hydroxy-8-(4-(1-phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)-octanoamide (Compound 34)

Step 24a. (R)—Methyl 8-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)octanoate (Compound 113-34) [0235] The title compound 113-34 was prepared as a solid (110 mg, 55%) from compound 112 (145 mg, 0.4 mmol) and 8-amino-octanoate hydrochloride (250 mg, 1.2 mmol) using a procedure similar to that described for compound 113-32 (Example 22): LCMS: 500 [M+H]⁺.

Step 24b. (R)—N-Hydroxy-8-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzalamino)-octanoamide (Compound 34) [0236] The title compound 34 was prepared as a pale yellow solid (41 mg, 57%) from compound 113-34 (110 mg, 0.22 mmol) and NH₂OH/MeOH (5 mL, 8.85 mmol) using a procedure similar to that described for compound 30-21 (Example 22): LCMS: 501 [M+H]⁺, 1 ¹H NMR (DMSO-d₆): δ 1.24 (s, 8H), 1.46 (m, 4H), 1.53 (d, J=6.9 Hz, 3H), 1.94 (t, J=6.9 Hz, 2H), 3.70 (s, 2H), 5.50 (m, 1H), 7.07 (s, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.30 (t, J=7.2 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H).
Example 25
Preparation of (R)-2-\((4-(4-(1-(4-fluorophenyl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)\)-N-hydroxyacetamide (Compound 37)

Step 25a. (R)—(N-(1-(4-Fluorophenyl)ethyl)-6-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 408)

A mixture of compound 404 (2.59 g, 10.0 mmol) and (R)-1-(4-Fluorophenyl)ethanamine (2.75 g, 20.0 mmol) in n-BuOH (30 mL) was stirred at 140°C overnight. The mixture was cooled, filtered, washed with Et2O to afford the product 408 as a yellow solid (2.3 g, 63%). LCMS: 363 [M+1]+.

Step 25b. (R)-4-(4-(1-(4-Fluorophenyl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (Compound 409)

To a solution of compound 408 (2.1 g, 5.6 mmol) in dichloromethane (150 mL) was added dropwise a solution of BF3·OEt2 (5.7 mL, 15.5 mmol) in dichloromethane (190 mL) at 0°C under nitrogen over 1 hour. After the addition was completed, the mixture was allowed to warm to room temperature and stirred overnight. Then 20 mL of water was added at 20°C. The mixture was warmed to room temperature, extracted with ethyl acetate (150 mL×3), washed with brine, filtered and concentrated to give the product 409 as a yellow solid (1.6 g, 81%). LCMS: 349 [M+1]+.

Step 25c. (R)-Ethyl 2-\((4-(4-(1-(4-fluorophenyl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)\) acetate (Compound 410-37)

To a mixture of compound 409 (522 mg, 1.5 mmol) and KHCO3 (345 mg, 2.5 mmol) in N,N-dimethylformamide (5.0 mL) was added Ethyl 7-bromohexanoate (356 mg, 1.5 mmol) and the mixture was stirred at 70°C for 20 hours. DMF was removed under reduced pressure at 50°C and then 30 mL of ethyl acetate was added. The organic layer was washed with water, dried over anhydrous Na2SO4, filtered, concentrated to give compound 410-37 (385 mg, 51%). LCMS: 505 [M+1]+.

Step 25d. (R)-2-(4-(1-(4-Fluorophenyl)ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)-N-hydroxyacetamide (Compound 37)

To a flask containing compound 410-37 (170 mg, 0.33 mmol) was added the saturated solution of hydroxylamine in methanol (5.0 mL). The mixture was stirred at room temperature for 30 min. Then it was neutralized to pH 7 using acetic acid and concentrated. The residue was washed with water, evaporated to afford crude product that was purified by column chromatography. The product 37 was obtained as a white solid (40 mg, 25%). LCMS: 492 [M+1]+.1H NMR (DMSO-d6): δ 8.129–1.54 (m, 9H), 1.65–1.74 (m, 2H), 1.94 (s, J=7.5 Hz, 2H), 3.98 (s, J=6.3 Hz, 2H), 5.47 (s, J=8.1 Hz, 1H), 6.91 (s, 1H), 6.98 (d, J=9.3 Hz, 2H), 7.42–7.46 (m, 3H), 7.68 (d, J=8.7 Hz, 3H), 8.02 (s, 1H), 8.60 (s, 1H), 10.29 (s, 1H), 11.87 (s, 1H).

Example 26
Preparation of 7-(4-(4-(benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)-N-hydroxyhexanoamide (Compound 38)

Step 26a. N-Benzyl-6-(4-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 411)

A mixture of compound 404 (2.59 g, 10 mmol) and phenylmethanamine (3.21 g, 30 mol) in n-BuOH (30 mL) was stirred at 140°C overnight. The mixture was cooled, filtered, washed with Et2O to afford the product 411 as a yellow solid (3.0 g, 93%). LCMS: 331 [M+1]+.

Step 26b. 4-(4-(Benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol (Compound 412)

To a solution of compound 411 (2.5 g, 7.6 mmol) in dichloromethane (202 mL) was added a solution of BF3·OEt2 (7.6 mL, 20.7 mmol) in dichloromethane (253 mL) at 0°C under nitrogen over 1 hour. After the addition was completed, the mixture was allowed to warm to room temperature and stirred overnight. Then 20 mL of water was added at 20°C. The mixture was warmed to room temperature, extracted with ethyl acetate (150 mL×3), washed with brine, dried, filtered, concentrated to give the product 412 as a yellow solid (1.43 g, 59%). LCMS: 317 [M+1]+.

Step 26c. Ethyl 7-(4-(4-(benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)hexanoate (Compound 413-38)

To a mixture of compound 412 (300 mg, 0.9 mmol) and K2CO3 (248 mg, 1.8 mmol) in N,N-dimethylformamide (4.0 mL) was added ethyl 7-bromohexanoate (213 mg, 0.9 mmol) and the resulting mixture was stirred at 70°C for 20 h. DMF was removed under reduced pressure at 50°C and was diluted with 30 mL of ethyl acetate. The organic layer was washed with water, dried over anhydrous Na2SO4, filtered and concentrated to give compound 413-38 (150 mg, 35%). LCMS: 473 [M+1]+.

Step 26d. 7-(4-(4-(Benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxo)-N-hydroxyhexanoamide (Compound 38)

To a flask containing compound 413-38 (100 mg, 0.21 mmol) was added the saturated solution of hydroxylamine in methanol (4.0 mL). The mixture was stirred at room temperature for 30 min. Then it was neutralized to pH 7 using acetic acid. The mixture was concentrated under reduced pressure and the residue was washed with water, evaporated. The residue was purified by column chromatography to obtain the product as a white solid (40 mg, 42%). LCMS: 460 [M+1]+.1H NMR (DMSO-d6): δ 8.130–1.54 (m, 9H), 1.72 (t, J=8.1 Hz, 2H), 1.96 (s, J=7.2 Hz, 2H), 4.00 (t, J=6.0 Hz, 2H), 4.81 (d, J=4.5 Hz, 2H), 7.04 (d, J=9.0 Hz, 2H), 7.12 (s, 1H).
Example 27
Preparation of (R)—N-hydroxy-4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzamido (Compound 39)

[0245] A mixture of compound 110 (149 mg, 0.4 mmol) and NH₂OH/Methanol (3 mL, 5.31 mmol) was stirred at room temperature for 0.5 hour. The reaction mixture was neutralized with AcOH and concentrated. The residue was suspended in water and the resulting precipitate was isolated and dried to give crude product that was purified by preparative HPLC to give product 39 as a pale yellow solid (42 mg, 28%): LCMS: 574 [M+1]⁺; ¹H NMR (DMSO-d₆): δ 6.13 (d, J=7.2 Hz, 3H), 5.50 (m, 1H), 7.22 (m, 2H), 7.31 (t, J=7.5 Hz, 2H), 7.42 (d, J=7.5 Hz, 2H), 7.64 (m, 5H), 8.06 (s, 1H), 9.06 (s, 1H), 11.23 (s, 1H), 12.15 (s, 1H).

Example 28
(R,E)-N-Hydroxy-3-((4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)phenyl)acrylamide (Compound 42)

Step 28a. (R,E)-Methyl 3-((4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)phenyl)acrylamide (Compound 703-42)

[0246] A mixture of compound 506 (200 mg, 0.6 mmol) and 4-formylcinnamic acid (140 mg, 0.8 mmol) in 40 mL of methanol was refluxed for 1 hour. NaBH₄CN (50 mg, 0.8 mmol) was then added and the mixture was stirred for an additional 3 hours. Thiouyl chloride (0.5 mL) was added dropwise to the mixture and stirred for 3 hours. The reaction was monitored by TLC. Then the mixture was concentrated under reduced pressure. The residue was washed with water and filtered to obtain compound 703-42 as a yellow solid (208 mg, 68.8%). LCMS: 504 [M+1]⁺.

Step 28b. (R,E)-N-Hydroxy-3-((4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)phenyl)acrylamide (Compound 42)

[0247] A mixture of 703-42 (208.4 g, 0.41 mmol) and the saturated solution of hydroxylamine in methanol (1.77 mol/L, 10 mL) was stirred for 6 hours at room temperature. The mixture was adjusted to pH 7-8 with acetic acid. Solvent was removed and the residue was suspended in water, filtered and purified to give compound 42 as a yellow solid (0.060 g, 29.0%); mp: 265.1-294.1°C, LC-MS: 505 [M+1]⁺; ¹H NMR (300 MHz, DMSO-d₆): δ 1.49 (d, J=7.2 Hz, 3H), 4.32 (d, J=4.8 Hz, 2H), 5.45 (m, 1H), 6.30-6.50 (m, 1H), 6.60 (d, J=8.4 Hz, 2H), 6.75 (s, 1H), 7.16 (t, J=7.2 Hz, J=6.6 Hz, 1H), 7.27 (d, J=7.5 Hz, 2H), 7.30-7.60 (m, 10H), 7.96 (s, 1H), 8.95 (s, 1H), 10.68 (s, 1H), 11.64 (s, 1H).

Example 29
(R)—N-Hydroxy-4-((4-((1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)benzamido (Compound 43)

Step 29a. (R)-Methyl 4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)benzoate (Compound 706-43)

[0248] A mixture of compound 506 (200 mg, 0.6 mmol) and 4-formylbenzoic acid (120 mg, 0.8 mmol) in methanol (40 mL) was refluxed for 1 hour. NaBH₄CN (50 mg, 0.8 mmol) was then added to the mixture and stirred for another 2 hours. Thiouyl chloride (0.2 mL) was added dropwise, and the mixture was stirred for 3 hours. The reaction was monitored by TLC. Then the mixture was concentrated under reduced pressure and the residue was washed with water and filtered to obtain compound 706-43 as a yellow solid (267 mg, 93.0%). LCMS: 478 [M+1]⁺.

Step 29b. (R)—N-Hydroxy-4-((4-((4-(1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)phenylamino)methyl)benzamido (Compound 43)

[0249] A mixture of 706-43 (0.267 g, 0.56 mmol) and the saturated solution of hydroxylamine in methanol (1.77 mol/L, 8 mL) was stirred for 6 hours at room temperature. The mixture was adjusted to pH 7-8 with acetic acid and solvent was removed. The residue was diluted with water, filtered and purified to give compound 43 as a yellow solid (0.065 g, 24.3%); mp: 169.3-170.9°C, LC-MS: 479 [M+1]⁺; ¹H NMR (300 MHz, DMSO-d₆): δ 1.49 (d, J=7.2 Hz, 3H), 4.34 (d, J=5.4 Hz, 2H), 5.45 (m, 1H), 6.52 (t, J=6.0 Hz, 1H), 6.29 (d, J=8.7 Hz, 2H), 6.75 (s, 1H), 7.16 (t, J=7.5 Hz, 1H), 7.27 (t, J=7.2 Hz, 2H), 7.30-7.50 (m, 6H), 7.57 (d, J=7.8 Hz, 1H), 7.68 (d, J=8.1 Hz, 2H), 7.96 (s, 1H), 8.94 (s, 1H), 11.11 (s, 1H), 11.65 s, 1H).

Example 30
Preparation of (R)—N-hydroxy-4-((4-((1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)methyl)benzamido (Compound 44)

Step 30a. (R)-6-(4-(aminomethyl)phenyl)-N-(1-phenylethyl)-7H-pyrrrolo[2,3-d]pyrimidin-4-amine (Compound 801)

[0250] A mixture of compound 112 (500 mg, 1.38 mmol) in ammonia (60 mL) was stirred and heated to 110°C in a sealed system for 24 hours. The mixture was cooled to room temperature and resulting precipitate was isolated. The solution was diluted with water, adjusted to pH 2 and the resulting precipitate was isolated and dried to yield title compound 801 as a grey solid (204 mg, 43%): LCMS: 344 [M+1]⁺.

Step 30b. (R)-methyl-4-((4-((1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)benzylamino)methyl)benzoate (Compound 802-44)

[0251] A mixture of compound 801 (170 mg, 0.5 mmol), 4-formylbenzoic acid (75 mg, 0.5 mmol) and methanol (40 mL) was stirred and heated to reflux for 1 hour. NaBH₃CN (50 mg, 0.75 mmol) was then added and the mixture was stirred under reflux for 2 hours. After that, sulfuric dichloride (90 mg, 0.75 mmol) was added and the mixture was stirred under reflux for additional 5 hours. The solvent was removed under reduced pressure and the residue was washed with water to get the crude product which was purified by column chromatography to yield title compound 802-44 as a grey solid (220 mg, 86%): LCMS: 492 [M+1]⁺.

Step 30c. (R)—N-hydroxy-4-((4-((1-phenylethylamino)-7H-pyrrrolo[2,3-d]pyrimidin-6-yl)methyl)benzamido (Compound 44)

[0252] To compound 802-44 (150 mg, 0.3 mmol) was added freshly prepared hydroxylamine solution (1.7 mL, 3 mmol). The reaction mixture was stirred at 20°C. For 30
minutes and then warmed to room temperature. The reaction process was monitored by TLC. The mixture was neutralized with acetic acid and the resulting mixture was concentrated under reduced pressure to yield a residue which was purified by preparation HPLC to give the title compound 44 as a grey solid (24 mg, 18\%): LCMS: 493 [M+1]*; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta 1.56\) (d, J=6.9 Hz, 3H), 3.68 (d, J=12.9 Hz, 4H), 5.48 (m, 1H), 7.05 (s, 1H), 7.17 (t, J=7.8 Hz, 1H), 7.37 (t, J=7.2 Hz, 2H), 7.70 (m, 6H), 8.03 (s, 1H), 8.93 (s, 1H), 11.12 (s, 1H), 11.94 (s, 1H).

**Example 31**

Preparation of (R,E)-N-hydroxy-3-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)enzyamo)methyl)phenyl)acrylamide (Compound 45)

Step 31a. (R,E)-methyl 3-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyllamino)methyl)phenyl)acrylamide (Compound 802-44)

[0253] The title compound 802-45 was prepared (153 mg, 48\% yield) from 801 (211 mg, 0.62 mmol) and (E)-methyl 3-(4-formylphenyl)acrylate (118 mg, 0.62 mmol) using a procedure similar to that described for compound 802-44 (Example 30): LCMS: 517 [M+1]*.

Step 31b. (R,E)-N-hydroxy-3-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyllamino)methyl)phenyl)acrylamide (Compound 45)

[0254] The title compound 45 was prepared as a grey solid (40 mg, 26\% yield) from compound 802-45 (154 mg, 0.30 mmol) and freshly prepared hydroxylamine in methanol (1.7 mL, 3.0 mmol) using a procedure similar to that described for compound 802-44 (Example 30): LCMS: 518 [M+1]*; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta 1.50\) (d, J=7.2 Hz, 3H), 3.70 (d, J=6.9 Hz, 4H), 5.48 (t, J=9.6 Hz, 1H), 6.39 (d, J=15.9 Hz, 1H), 7.06 (s, 1H), 7.18 (t, 1H), 7.29 (m, 4H), 7.40 (d, J=7.5 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H), 7.82 (d, J=8.4 Hz, 1H), 8.04 (s, 1H), 12.00 (s, 1H).

**Example 32**

Preparation of (R)—N-hydroxy-4-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethoxybutanamide (Compound 49)

Step 32a. (R)-2-(4-(4-(1-Phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethanol (Compound 901)

[0255] A mixture of compound 112 (1.37 g, 3.78 mmol), 2-(piperazin-1-yl)ethanol (590 mg, 5.45 mmol) and potassium carbonate (1.07 g 7.56 mmol) in N,N-dimethylformamide (20 mL) was stirred at 50° C. overnight. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was washed with water, and dried to provide the title compound 901 as a brown solid (1.552 g, 90.2\%): LCMS: 457 [M+1]*; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta 1.50\) (d, J=7.2, 31H), 2.34 (m, 8H), 4.44 (s, 4H), 4.36 (s, 1H), 5.48 (m, 1H), 7.06 (s, 1H), 7.15 (t, J=7.5, 1H), 7.29 (m, 6H), 7.73 (d, J=8.1, 2H), 7.79 (d, J=8.4, 1H), 8.04 (s, 1H).

Step 32b. (R)-methyl 4-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethoxybutanamide (Compound 902-49)

[0256] To the solution of compound 901 (456 mg, 1 mmol) in DMF (20 mL) was added NaH (24 mg, 1 mmol) in ice bath temperature. The mixture was stirred at this temperature for 30 minutes, and then methyl 4-bromobutanamide (231 mg, 1.2 mmol) was added and the mixture was stirred at 50° C. overnight. The solvent was removed under reduced pressure to obtain the crude product which was purified by column chromatography to yield title compound 902-49 as a grey solid (225 mg, 40\%): LCMS: 481 [M+1]*.

Step 32c. (R)—N-hydroxy-4-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)methyl)piperazin-1-yl)ethoxybutanamide (Compound 49)

[0257] To compound 902-49 (147 mg, 0.377 mmol) was added freshly prepared hydroxylamine solution (4.3 mL, 7.5 mmol). The reaction was stirred at 0° C. for 30 minutes and then warmed to room temperature. The reaction process was monitored by TLC. The mixture was neutralized with acetic acid and the mixture was concentrated under reduced pressure to yield a residue which was purified by preparation HPLC to give the title compound 49 as a grey solid (70 mg, 48\%): LCMS: 482 [M+1]*; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta 1.50\) (d, J=6.3 Hz, 3H), 1.76 (s, 4H), 2.39 (m, 10H), 4.17 (s, 2H), 4.35 (s, 1H), 5.50 (t, J=7.5, 1H), 6.76 (s, 1H), 7.24 (m, 1H), 7.32 (m, 2H), 7.32 (m, 2H), 7.42 (m, 6H), 7.82 (d, J=8.1, 2H), 8.10 (s, 1H), 8.61 (s, 1H), 10.27 (s, 1H).

**Example 33**

Preparation of (R)—N-hydroxy-5-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethoxypentanamide (Compound 50)

Step 33a. (R)-methyl 5-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)(methyl)piperazin-1-yl)ethoxy)pentanamide (Compound 902-50)

[0258] The title compound 902-50 was prepared (131 mg, 29\% yield) from 901 (361 mg, 0.79 mmol) and 5-bromopentanamide (183 mg, 0.95 mmol) using a procedure similar to that described for compound 902-49 (Example 32): LCMS: 517 [M+1]*.

Step 33b. (R)—N-hydroxy-5-(2-(4-(4-(1-phenylethylamino)-7H-pyrido[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethoxypentanamide (Compound 50)

[0259] The title compound 50 was prepared as a grey solid (90 mg, 69\% yield) from compound 902-50 (130 mg, 0.23 mmol) and freshly prepared hydroxylamine in methanol (1.3 mL, 2.3 mmol) using a procedure similar to that described for compound 49 (Example 32): LCMS: 572 [M+1]*; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta 1.23\) (s, 2H), 1.50 (d, J=6.9 Hz, 3H), 1.78 (t, J=7.5 Hz, 2H), 2.41 (s, 8H), 3.30 (s, 2H), 3.48 (m, 3H), 4.17
Example 34

Preparation of (R)—N-hydroxy-6-(2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)-ethoxyhexanamide (Compound 51)

Step 34a. (R)-methyl 6-(2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)-ethoxyhexanoate (Compound 902-51)

[0260] The title compound 902-51 was prepared as a grey solid (192 mg, 40% yield) from 901 (375 mg, 0.82 mmol) and methyl 6-bromohexanoate (204 mg, 0.98 mmol) using a procedure similar to that described for compound 902-49 (Example 32): LCMS: 585 [M+1]⁺.

Step 34b. (R)—N-hydroxy-6-(2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)-ethoxyhexanamide (Compound 51)

[0261] The title compound 51 was prepared as a grey solid (120 mg, 63% yield) from compound 902-51 (190 mg, 0.33 mmol) and freshly prepared hydroxylamine in methanol (1.9 mL, 33 mmol) using a procedure similar to that described for compound 49 (Example 32): LCMS: 586 [M+1]⁺; ¹H NMR (DMSO-d₆) δ 1.00 (t, J=8.1 Hz, 2H), 1.31 (t, J=7.2 Hz, 2H), 1.50 (d, J=6.6 Hz, 3H), 1.78 (t, J=6.6 Hz, 2H), 2.37 (s, 8H), 3.48 (m, 3H), 4.17 (s, 2H), 4.35 (s, 1H), 5.50 (s, 1H), 6.75 (s, 1H), 7.18 (t, J=6.9 Hz, 1H), 7.29 (t, J=6.12 Hz, 1H), 7.42 (m, 5H), 7.81 (d, J=8.1 Hz, 1H), 8.04 (s, 1H), 8.60 (s, 1H), 10.22 (s, 1H).

Example 35

(R)—N-hydroxy-6-(1-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperidin-4-yl)-ethanolamine (Compound 1001)

[0262] To a solution of compound 112 (1.1 g, 3.0 mmol) in DMF (10 mL) was added 1.4-Dioka-8-aza-spiro[4.5]decane (1.0 g, 7.0 mmol). The reaction was stirred at 10°C for 1 hour. The solvent was evaporated under reduced pressure and the residue was washed with water, dried to obtain compound 1001 as a brown solid (1.2 g, 93% yield) LC-MS: 469 [M+1]⁺.

Step 35a. 6-{3-(4-(1,4-Dioxa-8-aza-spiro[4.5]decane)-(4-yl)-piperidin-4-yl)-piperidin-4-yl}-ethylamine (Compound 55)

Step 35b. 1-{3-(4-(1,4-Dioxa-8-aza-spiro[4.5]decane)-(4-yl)-piperidin-4-yl)-piperidin-4-yl)-ethylamine (Compound 1001)

[0263] A solution of compound 1001 (1.2 g, 2.6 mmol) in THF (20 mL) and 20% H₂SO₄ (40 mL) was stirred at 50°C for 4 hours. The mixture was neutralized by saturated NaHCO₃. The precipitate was isolated and filtrated, dried to afford 1002 (1.0 g, 92% yield). LC-MS: 426 [M+1]⁺.

Step 35c. 6-(1-{3-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl}-piperidin-4-ylamino)-hexanoic acid methyl ester (Compound 1003-55)

[0264] A solution of compound 1002 (130 mg, 0.31 mmol), 6-Amino-hexanoic acid methyl ester (46 mg, 0.31 mmol) and acetic acid (18.6 mg, 0.31 mmol) in 1,2-dichloro-ethane (10 mL) was treated with NaH(0.5) (92 mg, 1.2 mmol) and stirred at 25°C over night. Saturated NaHCO₃ (10 mL) was added to the reaction mixture and the solvent was evaporated under reduced pressure to leave a residue. The residue was dissolved in THF and filtrated. The filtrate was concentrated and the crude product was purified by TLC to obtain compound 1003-55 as a brown solid (120 mg, 71% yield): LCMS: 555 [M+1]⁺.

Step 35d. 6-(1-{3-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl}-piperidin-4-ylamino)-hexanoic acid hydroxyamide (Compound 55)

[0265] To compound 1003-55 (60 mg, 0.1 mmol) was added freshly prepared hydroxylamine solution (1.0 mL, 1.8 mmol). The reaction mixture was sonicated for 40 minutes. The reaction process was monitored by TLC. After the completion of the reaction, the mixture was neutralized with acetic acid. The mixture was concentrated under reduced pressure and the residue was washed with water and dried to give the title compound 55 as a yellow solid (42 mg, 70%): LCMS: 556 [M+1]⁺; ¹H NMR (DMSO-d₆) δ 1.25 (m, 6H), 1.48 (m, 5H), 1.53 (d, J=7.5 Hz, 4H), 1.98 (d, J=7.5 Hz, 3H), 2.59 (t, J=7.5 Hz, 3H), 2.79 (d, J=11.1 Hz 2H), 3.4 (s, 2H), 5.48 (m, 1H), 7.07 (s, 1H), 7.18 (s, 1H), 7.26 (m, 1H), 7.51 (m, 5H), 7.42 (m, 2H), 7.72 (d, J=8.1 Hz, 1H), 7.72 (d, J=8.1 Hz, 1H), 7.80 (d, J=8.1 Hz, 1H), 8.04 (s, 1H), 11.98 (s, 1H).

Example 36

(R)—N-hydroxy-7-(1-{3-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl}-piperidin-4-ylamino)heptanamide (Compound 56)

Step 36a. 7-{3-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl}-piperidin-4-ylamino)-heptanoic acid methyl ester (Compound 1003-56)

[0266] The title compound 1003-56 was prepared as a yellow solid (60 mg, 36% yield) from 1002 and 7-Amino-heptanoic acid methyl ester (94 mg, 0.588 mmol) using a procedure similar to that described for compound 1003-55 (Example 35): LC-MS: 569 [M+1]⁺.

Step 36b. 7-{3-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl}-piperidin-4-ylamino)-heptanoic acid methyl ester (Compound 56)

[0267] The title compound 56 was prepared as a yellow solid (30 mg, 50% yield) from compound 1003-56 (60 mg, 0.11 mmol) using a procedure similar to that described for compound 55 (Example 35): LC-MS: 570 [M+1]⁺; ¹H NMR (DMSO-d₆) δ 1.25 (m, 6H), 1.48 (m, 5H), 1.53 (d, J=7.5 Hz, 4H), 1.98 (d, J=8.1 Hz, 3H), 2.7 (t, J=6.9 Hz, 2H), 2.53 (d,
Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl-ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)
Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)

Example 39
Preparation of (R)—N-hydroxy-7-(2-(4-[4-(1-phenyl ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy)ethylamino)heptanoic acid (Compound 1101)

Step 38a. (R)-2-(4-(4-1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyacetronitrile (Compound 1101)

Step 38b. (R)-6-(4-(2-aminooethoxy)phenyl)-N-(1 phenethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 1102)

To a 0°C solution of compound 1 (0.954 g, 2.58 mmol) in THF (120 mL) was added 1,1′-dihydropyrene (0.294 g, 2.74 mmol) slowly. The reaction was warmed to room temperature on a water bath, mixed with 10 min, then 1:3 (H₂O: 15% NaOH:H₂O₂) was added, filtered, and evaporated to obtain 102 as white solid (0.788 g, 82.5%).

Example 38
Preparation of (R)—N-hydroxy-6-(2-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)ethylamino)hexanoate (Compound 59)

Step 38a. (R)-2-(4-(4-1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyacetronitrile (Compound 1101)

Step 38b. (R)-6-(4-(2-aminooethoxy)phenyl)-N-(1 phenethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Compound 1102)

Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)

Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)

Example 39
Preparation of (R)—N-hydroxy-7-(2-(4-[4-(1-phenyl ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy)ethylamino)heptanoic acid (Compound 60)

Step 39a. (R)-methyl 7-(3-(4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propylamino)heptanoate (Compound 1103-60)

Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)

Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)

Example 39
Preparation of (R)—N-hydroxy-7-(2-(4-[4-(1-phenyl ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy)ethylamino)heptanoic acid (Compound 60)

Step 39a. (R)-methyl 7-(3-(4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propylamino)heptanoate (Compound 1103-60)

Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)

Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)

Example 39
Preparation of (R)—N-hydroxy-7-(2-(4-[4-(1-phenyl ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy)ethylamino)heptanoic acid (Compound 60)

Step 39a. (R)-methyl 7-(3-(4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propylamino)heptanoate (Compound 1103-60)

Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)

Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)

Example 39
Preparation of (R)—N-hydroxy-7-(2-(4-[4-(1-phenyl ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenoxy)ethylamino)heptanoic acid (Compound 60)

Step 39a. (R)-methyl 7-(3-(4-(4-(1-phenethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)propylamino)heptanoate (Compound 1103-60)

Example 37
Preparation of (R)—N-hydroxy-8-(1-(4-(4-(1-phenyl ethy lamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)pyr erdin-4-ylamino)octanoate (Compound 57)

Step 37a: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrol o[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid methyl ester (Compound 1003-57)

Step 37b: 8-(1-[4-[4-(1-Phenyl-ethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-benzyl]-piperidin-4-ylamino)-octanoic acid hydroxide (Compound 57)
7.30 (t, J=5.5 Hz, 2H), 7.43 (d, J=6.9 Hz, 2H), 7.71 (d, J=9.0 Hz, 3H), 8.04 (s, 1H), 10.33 (s, 1H), 11.92 (s, 1H).

Example 40
Preparation of (R) — N-hydroxy-8-(2-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)ethylamino)octanamide (Compound 61)

Step 40a. (R)-methyl 8-(3-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)propyl)octanamide (Compound 1103-61)

[0276] The title compound 1103-61 was prepared (95 mg, 16% yield) from 1102 (400 mg, 1.07 mmol) and 8-bromoocutanamide (507 mg, 2.14 mmol) using a procedure similar to that described for compound 1103-59 (Example 38); LC-MS: 530 [M+1]+.

Step 40b. (R) — N-hydroxy-8-(2-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)ethylamino)octanamide (compound 61)

[0277] The title compound 61 was prepared (55 mg, 59% yield) from compound 1103-61 (95 mg, 0.17 mmol) using a procedure similar to that described for compound 59 (Example 38); LC-MS: 531 [M+1]+, 1H NMR (DMSO-d6) δ 1.26 (s, 6H), 1.42-1.53 (m, 7H), 1.90 (t, J=6.6 Hz, 2H), 2.81 (t, J=6.6 Hz, 2H), 3.14-3.18 (m, 2H), 4.17 (s, 2H), 5.50 (q, J=6.9 Hz, 1H), 6.95 (s, 1H), 7.04 (d, J=6.0 Hz, 2H), 7.15-7.20 (m, 1H), 7.50 (t, J=5.5 Hz, 2H), 7.43 (d, J=6.9 Hz, 2H), 7.71 (d, J=9.0 Hz, 3H), 8.04 (s, 1H), 10.32 (s, 1H), 11.92 (s, 1H).

Example 41
Preparation of (R) — N-hydroxy-6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)hexanamide (Compound 66)

Step 41a. (R)-ethyl 6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)hexanoate (Compound 1201-66)

[0278] A mixture of compound 506 (500 mg, 1.52 mmol), ethyl 6-bromohexanoate (338.7 mg, 1.52 mmol) and DMF (15 mL) was stirred for 12 h at 50 °C. The solvent was removed under high vacuum and the crude product purified by prep-HPLC to provide target compound 1201-66 (80 mg, 10%) as a yellow solid. LCMS: 472 [M+1]+.

Step 41b. (R) — N-hydroxy-6-(4-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)hexanamide (Compound 66)

[0279] A mixture of compound 1201-66 (80 mg, 0.17 mmol) and freshly prepared NH2OH solution (1.77 M, 4 mL) was stirred for 15 min at room temperature. The mixture was adjusted to pH=7.0 with AcOH and the solvent was removed. The solid was added with water, filtered and dried to provide compound 66 as a yellow solid (50 mg, 60%); m.p. 207–217 °C, LCMS: 473 [M+1]+, 1H NMR (DMSO-d6) δ 1.36 (m, 2H), 1.51-1.53 (d, 7H, J=7.2 Hz), 1.96 (t, 2H, J=6.9 Hz), 3.03 (m, 2H), 4.53-5.53 (m, 1H), 5.81 (t, 1H, J=5.4 Hz), 6.62 (d, 2H, J=8.4 Hz), 7.79 (s, 1H), 7.19 (m, 1H), 7.32 (m, 2H), 7.43 (m, 2H), 7.53 (d, 2H, J=7.2 Hz), 7.64 (d, 1H, J=7.8 Hz), 7.99 (s, 1H), 8.69 (s, 1H), 10.37 (s, 1H), 11.71 (s, 1H).

Example 42
Preparation of (R) — N-hydroxy-7-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)heptanamide (Compound 67)

Step 42a. (R)-ethyl 7-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)heptanamide (Compound 1201-67)

[0280] The title compound 1201-67 was prepared as a yellow solid (105 mg, 14% yield); m.p. 256 (500 mg, 1.52 mmol) and ethyl 7-bromohexanamide (360 mg, 1.52 mmol) using a procedure similar to that described for compound 1201-66 (Example 41); LC-MS: 486 [M+1]+.

Step 42b. (R) — N-hydroxy-7-(4-(1-phenylethylamino)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxyl)heptanamide (Compound 67)

[0281] The title compound 67 was prepared as a yellow solid (85 mg, 86% yield) from compound 1201-67 (303 mg, 0.21 mmol) and freshly prepared hydroxylamine methanol solution (1.77 M, 5 mL) using a procedure similar to that described for compound 66 (Example 41); m. p. 125–130 °C, LCMS: 473 [M+1]+, 1H NMR (DMSO-d6) δ 1.29 (m, 4H), 1.41-1.51 (d, 7H, J=7.2 Hz), 1.96 (m, 2H), 3.03 (m, 2H), 5.43-5.53 (m, 1H), 5.81 (t, 1H, J=5.4 Hz), 6.62 (d, 2H, J=8.4 Hz), 6.79 (s, 1H), 7.19 (m, 1H), 7.32 (m, 2H), 7.43 (m, 2H), 7.53 (d, 2H, J=7.2 Hz), 7.64 (d, 1H, J=7.8 Hz), 7.98 (s, 1H), 8.67 (s, 1H), 10.34 (s, 1H), 11.70 (s, 1H).

Biological Assays:

[0282] As stated herebeforein the derivatives defined in the present invention possess anti-proliferation activity. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) An In Vitro Assay which Determines the Ability of a Test Compound to Inhibit a Receptor Tyrosine Kinase.

[0283] The ability of compounds to inhibit receptor kinase (EGFR, HER2/ErbB2, and VEGFR2) activity was assayed using HTScan™ Receptor Kinase Assay Kits (Cell Signaling Technologies, Danvers, Mass.). EGFR tyrosine kinase was obtained in partially purified form from GST-kinase fusion protein which was produced using a baculovirus expression system from a construct expressing human EGFR (His672-Ala1210) (GenBank Accession No. NM_001229) with an amino-terminal GST tag. HER2/ErbB2 tyrosine kinase was produced using a baculovirus expression system from a construct containing a human HER2/ErbB2 cDNA (GenBank Accession No. NM_004448) fragment (Lys672-Val1255) amino-terminally fused to a GST tag. VEGFR2 tyrosine kinase was produced using a baculovirus expression system from a construct containing a human VEGFR2 cDNA kinase domain (Asp805-Val1356) (GenBank accession No. AF035121) fragment amino-terminally fused to a GST-HIS6-Thrombin cleavage site. The proteins were purified by one-step affinity chromatography using glutathione-agarose. An anti-phosphotyrosine monoclonal antibody, P-Tyr-100, was used to detect phosphorylation of biotinylated substrate peptides (EGFR, Biotin-PTP1B (Tyr96); HER2/ErbB2, Biotinylated FLT3 (Tyr98); VEGFR2, Biotin-Gastrin Precursor (Tyr87)). Enzymatic activity was tested in 30 nM
HEPES, 5 mM MgCl₂, 5 mM MnCl₂, 200 μM ATP, 1.25 mM DTT, 3 μM Na₂VO₄, 1.5 mM peptide, and 50 ng EGF Receptor Kinase. Bound antibody was detected using the DELFIA system (PerkinElmer, Wellesley, Mass.) consisting of DELFIA® Europium-labeled Anti-mouse IgG (PerkinElmer, #AD1024), DELFIA® Enhancement Solution (PerkinElmer, #1244-105), and a DELFIA® Streptavidin coated, 96-well Plate (PerkinElmer, AAAND-6005). Fluorescence was measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data were plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

[0284] Test compounds were dissolved in dimethylsulfoxide (DMSO) to give a 20 mM working stock concentration. Each assay was setup as follows: Added 100 μl of 10 mM ATP to 1.25 ml 6 mM substrate peptide. Diluted the mixture with D₂O to 2.5 ml to make 2x ATP/substrate cocktail ([ATP] = 400 mM, [substrate]=3 mM). Immediately transfer enzyme from −80°C to ice. Allowed enzyme to thaw on ice. Microcentrifuge briefly at 4°C to bring liquid to the bottom of the vial. Returned immediately to ice. Added 10 μl of DTT (1.25 mM) to 2.5 ml of 4xHTScan™ Tyrosine Kinase Buffer (240 mM HEPES pH 7.5, 20 mM MgCl₂, 20 mM MnCl₂, 12 mM Na₂VO₄) to make DTT/Kinase buffer. Transfer 1.25 ml of DTT/Kinase buffer to enzyme tube to make 4x reaction cocktail (enzyme=4 ng/μl in 4x reaction cocktail). Incubate 12.5 μl of the 4x reaction cocktail with 12.5 μl/μl of prediluted compound of interest (usually around 10 μM) for 5 minutes at room temperature. Added 25 μl of 2x ATP/substrate cocktail to 25 μl/well preincubated reaction cocktail/compound. Incubated reaction plate at room temperature for 30 minutes. Added 50 μl/well Stop Buffer (50 mM EDTA, pH 8) to stop the reaction. Transferred 25 μl of each reaction and 75 μl D₂O well to a 96-well streptavidin-coated plate and incubated at room temperature for 60 minutes. Washed three times with 200 μl/well PBS/T (PBS, 0.05% Tween-20). Diluted primary antibody, Phospho-Tyrosine mAb (P-Tyr-100), 1:1000 in PBS/T with 1% bovine serum albumin (BSA). Added 100 μl/well primary antibody. Incubated at room temperature for 60 minutes. Washed three times with 200 μl/well PBS/T. Diluted Europium labeled anti-mouse IgG 1:1500 in PBS/T with 1% BSA. Added 100 μl/well diluted antibody. Incubated at room temperature for 30 minutes. Washed five times with 200 μl/well PBS/T. Added 100 μl/well DELFIA® Enhancement Solution. Incubated at room temperature for 5 minutes. Detected 615 nm fluorescence emission with appropriate Time-Resolved Plate Reader.

(b) An In Vitro Assay which Determines the Ability of a Test Compound to Inhibit the EGF-Stimulated EGFR Phosphorylation.

[0285] Allowed A431 cell growth in a T75 flask using standard tissue culture procedures until cells reach near confluence (~1.5×10⁶ cells; D-MEM, 10% FBS). Under sterile conditions dispensed 100 μl of the cell suspension per well in 96-well microplates (x cells plated per well). Incubated cells and monitor cell density until confluence is achieved with well-to-well consistency; approximately three days. Removed complete media from plate wells by aspiration or manual displacement. Replaced media with 50 μl of prewarmed serum free media per well and incubated 4 to 16 hours. Made two fold serial dilutions of inhibitor using prewarmed D-MEM so that the final concentration of inhibitor range from 10 μM to 90 μM. Removed media in A431 cell plate. Added 100 μl of serial diluted inhibitor into cells and incubate 1 to 2 hours. Removed inhibitor from plate wells by aspiration or manual displacement. Added either serum free media for resting cells (mock) or serum free media with 100 ng/ml EGF. Used 100 μl of resting/activation media per well. Allowed incubation at 37°C for 7.5 minutes. Removed activation or stimulation media manually or by aspiration. Immediately fixed cells with 4% formaldehyde in 1xPBS. Allowed incubation on bench top for 20 minutes at RT with no shaking. Washed five times with 1xPBS containing 0.1% Triton X-100 for 5 minutes per Wash. Removed fixing Solution. Using a multi-channel pipettor, added 200 μl of Triton Washing Solution (1xPBS+0.1% Triton X-100). Allowed wash to shake on a rotator for 5 minutes at room temperature. Repeated washing steps 4 more times after removing wash manually. Using a multi-channel pipettor, blocked cells/wells by adding 100 μl of LI-COR Odyssey Blocking Buffer to each well. Allowed blocking for 90 minutes at RT with moderate shaking on a rotator. Added the two primary antibodies into a tube containing Odyssey Blocking Buffer. Mixed the primary antibody solution well before addition to wells (Phospho-EGFR Tyr1045, Rabbit; 1:100 dilution; Cell Signaling Technology, 2237; Total EGF, Mouse; 1:500 dilution; Biosource International, AHR5062). Removed blocking buffer from the blocking step and added 40 μl of the desired primary antibody or antibodies in Odyssey Blocking Buffer to cover the bottom of each well. Added 100 μl of Odyssey Blocking Buffer only to control wells. Incubated with primary antibody overnight with gentle shaking at RT. Washed the plate five times with 1xPBS+0.1% Tween-20 for 5 minutes at RT with gentle shaking, using a generous amount of buffer. Using a multi-channel pipettor, added 200 μl of Tween Washing Solution. Allowed wash to shake on a rotator for 5 minutes at RT. Repeated washing steps 4 more times. Diluted the fluorescently labeled secondary antibody in Odyssey Blocking Buffer (Goat anti-mouse IRDye™ 680 (1:200 dilution; LI-COR Cat. #926-32220) Goat anti-rabbit IRDye™ 800CW (1:800 dilution; LI-COR Cat. #926-32211). Mixed the antibody solutions well and added 40 μl of the secondary antibody solution to each well. Incubated for 60 minutes with gentle shaking at RT. Protected plate from light during incubation. Washed the plate five times with 1xPBS+0.1% Tween-20 for 5 minutes at RT with gentle shaking, using a generous amount of buffer. Using a multi-channel pipettor, added 200 μl of Tween Washing Solution. Allowed wash to shake on a rotator for 5 minutes at RT. Repeated washing steps 4 more times. After final wash, removed wash solution completely from wells. Turned the plate upside down and tap or blot gently on paper towels to remove traces of wash buffer. Scanned the plate with detection in both the 700 and 800 channels using the Odyssey Infrared Imaging System (700 nm detection for IRDye™ 680 antibody and 800 nm detection for IRDye™ 800CW antibody). Determined the ratio of total to phosphorylated protein (700/800) using Odyssey software and plot the results in Graphpad Prism (v4.0a). Data were plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

(c) An In Vitro Assay which Determines the Ability of a Test Compound to Inhibit HDAC Enzymatic Activity.

[0286] HDAC inhibitors were screened using an HDAC fluorometric assay kit (AK-500, Biomol, Plymouth Meeting, Pa.). Test compounds were dissolved in dimethylsulfoxide (DMSO) to give a 20 mM working stock concentration. Fluorescence was measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data were
plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm. Each assay was setup as follows: Defrosted all kit components and kept on ice until use. Diluted HeLa nuclear extract 1:9 in Assay Buffer (50 mM Tris/Cl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl2). Prepared dilutions of Trichostatin A (TSA, positive control) and tested compounds in assay buffer (5× of final concentration). Diluted Fluor de LysTM Substrate in assay buffer to 100 μM (50 fold=2× final). Diluted Fluor de LysTM developer concentrate 20-fold (e.g. 50 μl plus 950 μl Assay Buffer) in cold assay buffer. Second, diluted the 0.2 mM Trichostatin A 100-fold in the 1× Developer (e.g. 10 μl in 1 ml) final Trichostatin A concentration in the 1× Developer=2 μM, final concentration after addition to HDAC/Substrate reaction=1 μM). Added Assay buffer, diluted trichostatin A or test inhibitor to appropriate wells of the microtiter plate. Added diluted HeLa extract or other HDAC sample to all wells except for negative controls. Added diluted Fluor de LysTM Substrate and the samples in the microtiter plate to equilibrate to assay temperature (e.g. 25 or 37°C). Initiated HDAC reactions by adding diluted substrate (25 μl) to each well and mixing thoroughly. Allowed HDAC reactions to proceed for 1 hour and then stopped them by addition of Fluor de LysTM Developer (501). Incubated plate at room temperature (25°C) for 10-15 min. Read samples in a microtiter-plate reading fluorometer capable of excitation at a wavelength in the range 350-380 nm and detection of emitted light in the range 440-460 nm.

**TABLE B**

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**[0288]** The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

**[0289]** While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

1. A compound represented by formula (I) or (II):

![Formula I](image1)

![Formula II](image2)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

Ar is aryl, substituted aryl heteroaryl or substituted heteroaryl;

Q is absent or substituted or unsubstituted alkyl;
X is O, S, NH, or alkylamino;
Z₂ is O, S, or NR₄, where R₄ is hydrogen, alkyl or substituted alkyl;
Y₂ is N or CR₂₀, where R₂₀ is selected from hydrogen, halogen, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;
B linker;
C is selected from:

(a) ![Diagram](attachment:diagram1.png)

where W is O or S; Y is absent, N, or CH; Z is N or CH; R₂ and R₃ are independently hydrogen, OR', aliphatic or substituted aliphatic, wherein R' is hydrogen, aliphatic, substituted aliphatic or acyl; provided that if R₂ and R₃ are both present, one of R₂ or R₃ must be OR' and if Y is absent, R₃ must be OR'; and R₆ is hydrogen, acyl, aliphatic or substituted aliphatic;

(b) ![Diagram](attachment:diagram2.png)

where W is O or S; J is O, NH or NCH₂; and R₁₀ is hydrogen or lower alkyl;

(c) ![Diagram](attachment:diagram3.png)

where W is O or S; Y₁ and Z₁ are independently N, C or CH; and

where Z, Y, and W are as previously defined; R₁, and R₂ are independently selected from hydrogen or aliphatic; R₃, R₄, and R₅ are independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkylsulfonyl, CF₃, CN, N₃, NO₂, sulfonyl, acyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic.

2. A compound according to claim 1, wherein B is a direct bond or straight- or branched-, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkylnalylalkyl, alkynalylalkenyl, alkynalylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylheteroaryl, alkylheteroaryl, or alkylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, SO₂, N(R₄), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R₄ is hydrogen, acyl, aliphatic or substituted aliphatic.

3. A compound according to claim 1 represented by formula (III):

![Diagram](attachment:diagram4.png)
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein \( M_1 \) is absent, O, S, NH, alkylamino, \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl, \( C_2-C_6 \) alkynyl, aryl, heteroaryl, heterocyclic, SO, SO₂ or \( O=C=O; M_2 \) is absent, \( C_1-C_9 \) alkyl, O, NH, alkylamine, heterocyclic, aryl, heteroaryl, or \( O=C=O; M_3 \) is absent, O, NH, alkylamino, S, SO, SO₂, CO, \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl, \( C_2-C_6 \) alkynyl, aryl, heteroaryl, or heterocyclic; \( M_4 \) is absent, O, NH, alkylamino, heteroaryl, heterocyclic or aryl; \( M_5 \) is absent, \( C_1-C_9 \) alkyl, \( C_2-C_9 \) alkenyl, \( C_2-C_9 \) alkynyl, heteroaryl, heterocyclic or aryl; \( R', Q, Ar \) and \( R_a \) are as previously defined in claim 1.

4. A compound according to claim 1 represented by formula (IV):

![Chemical Structure (IV)]

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein \( n \) is 0-9; \( R', Q, Ar \) and \( R_a \) are as previously defined in claim 1.

5. A compound according to claim 1 represented by formula (V):

![Chemical Structure (V)]

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein \( n \) is 0-9; \( G \) is absent, O, S, SO, SO₂, C(O)NH and N(R_a); and \( R', Q, Ar \) and \( R_a \) are as previously defined in claim 1.

6. A compound according to claim 1 represented by formula (VI):

![Chemical Structure (VI)]
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, where \( r \) is 1-7; \( U \) is \( N(R_s) \); \( Q, Ar \) and \( R_s \) are as previously defined in claim 1.

7. A compound according to claim 1 represented by formula (VII):

\[
\text{(VII)} \\
\begin{align*}
\text{HN}_1 & - \text{SA} - \text{U} - \text{N}_1\text{N} - \text{Y}, \text{O} - \text{R-6}
\end{align*}
\]

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, where \( m \) is 0-6; \( m \) is 1-4; \( G \) is absent, O, S, SO, SO_2, and N(R_s); \( R', Q, Ar \) and \( R_s \) are as previously defined in claim 1.

8. A compound according to claim 1 represented by formula (VIII):

\[
\text{(VIII)} \\
\begin{align*}
\text{HN}_1 & - \text{SA} - \text{U} - \text{N}_1\text{N} - \text{Y}, \text{O} - \text{R-6}
\end{align*}
\]

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, where \( m \) and \( n \) are independently 1-10; \( U \) is \( N(R_s) \); \( R', Q, Ar \) and \( R_s \) are as previously defined in claim 1.

9. A compound according to claim 1 selected from the compounds delineated in Table A or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

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<th>Compound #</th>
<th>Structure</th>
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TABLE A-continued

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### TABLE A-continued

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TABLE A-continued

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</table>
10. A pharmaceutical composition comprising as an active ingredient a compound of claim 1 and a pharmaceutical acceptable carrier.

11. A method of treating a PTK related disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 10.

12. The method of claim 11, wherein said PTK related disease or disorder is a cell proliferative disorder.


15. A method of treating both PTK and HDAC mediated diseases comprising administering to a subject in need thereof a pharmaceutical composition of claim 10.

* * * * *